No. 77- 956

IN THE

Supreme Court of the United States

October Term, 1977

PARKE, DAVIS & COMPANY,

Petitioner,

v.

JOSEPH A. CALIFANO, Secretary of Health, Education, and Welfare, *et al.*,

Respondents.

APPENDICES TO THE PETITION FOR A WRIT OF CERTIORARI

CLARK M. CLIFFORD
THOMAS RICHARD SPRADLIN
ALFRED W. CORTESE, JR.
815 Connecticut Avenue, N.W.
Washington, D. C. 20006

JOHN H. PICKERING
MICHAEL S. HELFER
1666 K Street, N.W.
Washington, D. C. 20006
Counsel for Petitioner

CHARLES E. LENTS
Joseph Campau at the River
Detroit, Michigan 48232

CLIFFORD, GLASS, MCILWAIN & FINNEY
815 Connecticut Avenue, N.W.
Washington, D. C. 20006

WILMER, CUTLER & PICKERING
1666 K Street, N.W.
Washington, D. C. 20006
Of Counsel

January 4, 1978

INDEX OF APPENDICES

APPENDIX A

No. 77-1224

UNITED STATES COURT OF APPEALS

FOR THE SIXTH CIRCUIT

PARKE, DAVIS & COMPANY,
Plaintiff-Appellee,

v.

JOSEPH A. CALIFANO, Secretary of Health, Education and Welfare,

DONALD KENNEDY, Commissioner of Food and Drugs, and the FOOD AND DRUG ADMINISTRATION,
Defendants-Appellants,

and

UNITED STATES OF AMERICA,
Appellant.

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR FOR THE EASTERN DISTRICT OF MICHIGAN, SOUTHERN DIVISION.

Decided and Filed October 26, 1977

Before: PHILLIPS, Chief Judge; WEICK and LIVELY, Circuit Judges.

LIVELY, Circuit Judge. The question in this case is whether the district court properly enjoined enforcement actions by the Food and Drug Administration (FDA) which were instituted as libels for the seizure of drugs in warehouses of the plaintiff, Parke, Davis & Company (Parke Davis). The appellants contend that the judgment

indication that OTC sale would not provoke regulatory action. The acting director of a Division of the Bureau of Drugs wrote Parke Davis on March 11, 1975 that FDA was deferring action on its supplemental NDA pending completion of OTC review under the procedures prescribed in the May 11, 1972 rule. One week later the Associate Chief Counsel for Enforcement of FDA wrote Parke Davis in response to its February 28th inquiry (the Yingling letter). The Yingling letter contained the following language:

> When the FDA began the OTC Review we said that we would institute legal action against new products only where they were fraudulent or represented a health hazard. Since the new product in question (Benylin Cough Syrup) conforms to the recommendations of the OTC Panel considering this particular type of product and has actually been marketed as a prescription preparation (Benylin Expectorant) for a significant period of time, there would be almost no possibility that we would institute legal action at this time. Faced with the limited resources and higher priority issues, the FDA does not intend to institute wholesale enforcement action except to require compliance with published monographs. This is the only position that the Agency can take as it seeks to obtain more efficient uses of its available resources.
>
> You realize, of course, if Benylin Cough Syrup is marketed now, your company assumes the risk that the Agency may not adopt this panel's categorization of diphenhydramine hydrochloride as generally recognized as safe and effective or that the FDA may eventually require different labeling from that which is presently accepted by the panel.

On May 9, 1975 FDA published new procedure and practice regulations in which it adopted a policy of refrain-

ing from granting informal exemptions. In September 1975 Parke Davis began marketing Benylin Cough Syrup as an OTC antitussive. On December 4, 1975 the FDA published a notice of proposed rule making which evolved into final regulations published August 4, 1976 at 41 Fed. Reg. 32580. The preamble to the August 4 publication provided that an OTC drug product which contained an active ingredient previously limited to prescription use which is classified by an OTC review panel in category I (generally recognized as safe and effective and not misbranded) "shall be considered a new drug if marketed before the date of publication in the FEDERAL REGISTER of a proposed monograph for the ingredient." The preamble further provided that such a product "may be marketed after the date of publication of a proposed monograph in the FEDERAL REGISTER, but before the effective date of a final monograph, subject to the risk that the commissioner may not accept a panel's recommendation but adopt a different position that could require relabeling, recall, or other regulatory action." The actual regulations, which now appear at 21 CFR § 310.200 and § 330.13 provide that an OTC drug product which contains an active ingredient that was limited on or after May 11, 1972 to prescription use and is under OTC review and has not thereafter been exempted from such limitation,

> . . . which is marketed after the date of publication in the FEDERAL REGISTER of a proposed monograph but prior to the effective date of a final monograph shall be subject to the risk that the Commissioner may not accept the panel's recommendation and may instead adopt a different position that may require relabeling, recall, or other regulatory action. The Commissioner may state such position at any time by notice in the FEDERAL REGISTER, either separately or as part of another document;

appropriate regulatory action will commence immediately and will not await publication of a final monograph. Marketing of such a product with a formulation or labeling not in accord with a proposed monograph or tentative final monograph also may result in regulatory action against the product, the marketer, or both.

On September 8, 1976 Parke Davis was advised by the FDA that its supplemental NDA was not approvable and therefore could not be filed as a supplemental application. On September 9, 1976 the commissioner published a proposed order which contained the monograph developed by the advisory panel classifying DPH as category I. In the preamble to the September 9 order the commissioner stated that the status of DPH as an antitussive would be determined through a supplemental NDA procedure. Parke Davis protested the September 8, 1976 notice that its supplemental NDA was not approvable, following procedures prescribed in 21 CFR 314.110(d). On November 22, 1976 the appropriate officer at FDA signed a notice of proposed denial of Parke Davis' supplemental NDA which had been filed over protest. Parke Davis was notified that it might request a hearing, and the hearing has now been scheduled. On the same day, November 22, 1976, the commissioner issued an order styled "Notice of Decision on Diphenhydramine as an Antitussive." This order contained his dissent from the panel recommendations on DPH as an antitussive and stated that products containing DPH marketed over the counter would be subject to regulatory action. Both the commissioner's November 22 dissent and the November 22 proposed NDA denial were published in the Federal Register on November 30, 1976.

The present action was filed in the United States District Court for the Eastern District of Michigan on November

29, 1976. Three days prior thereto FDA personnel had been instructed to prepare draft complaints for seizure of Benylin Cough Syrup in 13 districts and letters to the United States attorneys in those districts recommending institution of seizure actions pursuant to 21 U.S.C. § 334. On November 30 and December 1, 1976 complaints were filed and seizures of Benylin Cough Syrup were effected in the Northern District of Texas, the Northern District of Illinois and the District of Minnesota. The district court in the present action isued a temporary restraining order on December 1, 1976 and, after hearings on December 3rd and 8th, issued a preliminary injunction on the latter date. Shortly thereafter the district court filed a memorandum opinion setting forth its reasons for granting the injunction.

The district court found that Parke Davis had pursued two alternative methods in attempting to obtain FDA approval for over-the-counter sale of Benylin and that the Yingling letter constituted "de facto approval" of Parke Davis' proposal that it begin over-the-counter sales of Benylin following issuance of the preliminary monograph classifying DPH as safe and effective. The court further found that Parke Davis continued to sell Benylin over the counter contrary to the enforcement policy of FDA throughout most of 1976 "without provoking FDA enforcement action." Emphasizing Parke Davis' reliance on assurances in the Yingling letter that enforcement action was unlikely in view of the panel determination to place DPH in category I, the district court found that Parke Davis would suffer irreparable injury unless FDA were restrained, and that the action of FDA in threatening enforcement was arbitrary and capricious. The court found specifically that neither the proposed denial of the supplemental NDA nor the published dissent to the panel recommendations was a final decision, but concluded that the threatened enforcement action was agency action which was final since it had

a sufficiently direct and immediate effect on Parke Davis and that no other adequate remedy is provided by the Act.

The parties are in sharp disagreement as to what the district court actually held. The appellants contend that the trial court relied on a theory of estoppel, and argue that the doctrine of equitable estoppel may not be applied against the government. They also argue that the only agency action which the district court reviewed was the determination to utilize the seizure procedure provided by statute in an enforcement action, and contend that the district court has no jurisdiction to review such a determination. Parke Davis argues that the two actions of November 22, 1976 "purported to change the regulatory status of products containing DPH which were lawfully marketed, to subject those products to the threat of immediate regulatory action, and to do so contrary to the recommendations of the expert panel and without first affording interested persons an opportunity for a hearing." It is the assertion of the appellee that under the August 4 regulations, over-the-counter marketing of Benylin was lawful since the monograph had been published and the commissioner had not dissented.

The district court did not find that there had been a change in the status of the product, but appears to have relied upon the conclusion that FDA encouraged Parke Davis to market Benylin over the counter pending a final determination, and acquiesced in such marketing for nearly a year. The action which the district court found to be arbitrary and capricious was the decision of FDA to institute seizure actions pending final determination of the supplemental NDA application of Parke Davis. The district court avoided any finding with respect to the ultimate right of Parke Davis to market Benylin over the counter, but merely preserved its interim right to do so until a final decision is reached.

It is established in *Abbott Laboratories* v. *Gardner*, 387 U.S. 136 (1967), that Congress did not intend, in the enactment of the Food, Drug and Cosmetic Act and its amendments, to preclude all judicial review of final agency actions of the FDA except in the manner set forth in 21 U.S.C. § 371(f)(1).[2] Construing the Food, Drug and Cosmetic Act together with the Administrative Procedure Act, the Court concluded that the action of the FDA in promulgating industry-wide regulations was subject to pre-enforcement review under the "saving clause" of 21 U.S.C. § 371(f)(6).[3] It cannot be argued since *Abbott Laboratories* that district courts are totally without jurisdiction to conduct pre-enforcement review of agency actions. However, such review is limited.

In *Abbot Laboratories* the Supreme Court reaffirmed its earlier holding in *Ewing* v. *Mytinger & Casselberry*, 339 U.S. 594 (1950), and distinguished the two cases. In *Ewing* the plaintiff had been subjected to eleven seizures and libel actions by the FDA within a three-month period. It brought suit to have declared unconstitutional a provision of the Act which authorized the commissioner to file multiple actions for condemnation of drug products upon a finding, without a hearing, of probable cause to believe the drugs were being marketed in violation of the Act. The Court held that due process was satisfied by provisions of the

---

[2] 21 U.S.C. § 371(f)(1) provides in part:

Review of order

(f)(1) In a case of actual controversy as to the validity of any order under subsection (e) of this section, any person who will be adversely affected by such order if placed in effect at any time prior to the ninetieth day after such order is issued file a petition with the United States court of appeals for the circuit wherein such person resides or has his principal place of business, for a judicial review of such order.

[3] 21 U.S.C. § 371(f)(6) provides:

(6) The remedies provided for in this subsection shall be in addition to and not in substitution for any other remedies provided by law.

Act which permit the owner of the seized drugs to appear in the seizure action and have a full hearing in accordance with rules for proceedings in admiralty. The Court also noted that the owner of the seized drugs may procure consolidation of all pending seizure actions so that the issues may be decided at one trial. The section referred to in *Ewing*, now 21 U.S.C. § 334(b),[4] also provides for removal of seizure actions to a district near the claimant's principal place of business, and for trial by jury of issues of fact.

The Supreme Court pointed out in Ewing that a finding of probable cause to believe that a product is misbranded is of no effect by itself since a libel will not be instituted

[4]21 U.S.C. § 334(b) provides:

Procedure; multiplicity of pending proceedings

(b) The article, equipment, or other thing proceeded against shall be liable to seizure by process pursuant to the libel, and the procedure in cases under this section shall conform, as nearly as may be, to the procedure in admiralty; except that on demand of either party any issue of fact joined in any such case shall be tried by jury. When libel for condemnation proceedings under this section, involving the same claimant and the same issues of adulteration or misbranding, are pending in two or more jurisdictions, such pending proceedings, upon application of the claimant seasonably made to the court of one such jurisdiction, shall be consolidated for trial by order of such court, and tried in (1) any district selected by the claimant where one of such proceedings is pending; or (2) a district agreed upon by stipulation between the parties. If no order for consolidation is so made within a reasonable time, the claimant may apply to the court of one such jurisdiction, and such court (after giving the United States attorney for such district reasonable notice and opportunity to be heard) shall by order, unless good cause to the contrary is shown, specify a district of reasonable proximity to the claimant's principal place of business, in which all such pending proceedings shall be consolidated for trial and tried. Such order of consolidation shall not apply so as to require the removal of any case the date for trial of which has been fixed. The court granting such order shall give prompt notification thereof to the other courts having jurisdiction of the cases covered thereby.

unless the United States Attorney in the proper district agrees to file it upon a request of the FDA, and stated:

> Yet it has never been held that the hand of the government must be stayed until the courts have an opportunity to determine whether the government is justified in instituting suit in the courts. 339 U.S. at 599.

In *Abbott Laboratories* the Supreme Court stated that the decision in *Ewing* was "clearly correct" and described that decision as follows:

> This Court held that the owner could raise his constitutional, statutory, and factual claims in the libel actions themselves, and that the mere finding of probable cause by the Administrator could not be challenged in a separate action. 387 U.S. at 147.

When this action was filed in the district court Parke Davis had taken the necessary steps to obtain a final decision on its right to market Benylin over the counter by protesting the ruling that its supplemental NDA was not approvable. A hearing will be held before a final decision is rendered on that application, and the decision will be subject to judicial review by the appropriate court of appeals pursuant to 21 U.S.C. § 371(f)(1).

We conclude that the district court had no jurisdiction to review the decision of the FDA to initiate enforcement actions. That decision is indistinguishable from the finding of probable cause which the Supreme Court has held may not be challenged in a separate action. *Ewing, supra.*

Parke Davis argues in this court that the district court did more than review the decision of the commissioner to initiate enforcement proceedings. It contends that the district court acted properly under the Administrative Procedure Act to prevent irreparable injury from an arbitrary

and capricious action of the commissioner in seizing drug products which were being distributed over the counter as a matter of right following publication of the preliminary monograph without dissent. Parke Davis relies primarily on *Upjohn Co. v. Finch,* 303 F. Supp. 241 (W.D. Mich. 1969). In *Upjohn* the FDA revoked a certificate for marketing an antibiotic which had been approved for 12 years. No enforcement action was pending and no hearing was provided prior to revocation. *Upjohn* is distinguishable in at least two respects. First, the drug in question had been approved for sale—this was not in dispute. In the present case Benylin has never received final approval as an over-the-counter drug. The "switch-over" proceedings are still in progress, and a hearing is scheduled. The OTC Review was concluded with a decision adverse to Parke Davis. Secondly, in this case enforcement proceedings were pending in other jurisdictions when the district court issued its injunctive orders. Every issue raised in this case, including the question of whether the OTC Review regulations deprived Parke Davis of due process rights by failing to provide for a hearing and failing to contain guidelines for the commissioner in determining whether to accept or dissent from a panel monograph, could have been raised in the enforcement proceedings.

Thus Parke Davis had an adequate remedy, and the district court erred in holding that it did not. Parke Davis had the same remedy which was available to the distributor in *Ewing*—the statutory right to contest the seizure of its property in the libels, four of which had been filed before the injunction was entered in the present action. Parke Davis did not interpose defenses in any of these actions. These actions could have been consolidated for a single trial in a convenient district and Parke Davis could have raised the issues there which it sought to raise in the present action. In view of the fact that no final decision had been

made on the supplemental NDA, "it would be commonplace for the [enforcement] court to await an appropriate administrative declaration before it acted." *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 652 (1973). Instead of following statutory procedures which the Supreme Court said in *Ewing* were designed to afford relief, Parke Davis elected to seek the extraordinary remedy of injunction. Though the district court had jurisdiction under the Administrative Procedure Act to consider the complaint of Parke Davis, insofar as it questioned the regulations and procedures of the FDA as contrasted with the mere decision to initiate enforcement proceedings, it was an abuse of discretion to enjoin the FDA in the circumstances of this case where pending enforcement actions provided an opportunity for a full hearing before a court. In short, this case is controlled by *Ewing* v. *Mytinger & Casselberry* rather than *Abbott Laboratories* v. *Gardner* and *Upjohn Co.* v. *Finch.*

The judgment of the district court is reversed and the cause is remanded to the district court for dismissal of the complaint. Costs on appeal will be taxed to the appellee.

APPENDIX B

UNITED STATES DISTRICT COURT

EASTERN DISTRICT OF MICHIGAN
SOUTHERN DIVISION

CIVIL ACTION NO: 6-72464

PARKE, DAVIS & COMPANY,

Plaintiff,

v.

DAVID MATHEWS, Secretary of Health, Education, and Welfare,

SHERWIN GARDNER, Acting Commissioner of Food and Drugs,

THE FOOD AND DRUG ADMINISTRATION,

Defendants.

MEMORANDUM OPINION

Parke, Davis & Company, plaintiff, brings this action seeking a declaratory judgment that its product, Benylin Cough Syrup (Benylin), is not a "new drug" within the meaning of 21 U.S.C. § 321(p) and is not limited to distribution by prescription under 21 U.S.C. § 353(b). In the alternative, plaintiff seeks an order enjoining defendants from initiating enforcement action against over-the-counter (OTC) sale of Benylin pending final determination of Benylin's status by the Food and Drug Administration (FDA).

Shortly after the complaint was filed, defendants initiated seizures of Benylin at various wholesale distribution points. This court at that point granted an order temporarily restraining both the seizures of Benylin and its wholesale distribution. *See* Order dated December 1, 1976. A preliminary injunction was subsequently entered restraining defendants from instituting enforcement proceedings affecting the distribution of Benylin until thirty days after the FDA makes a final determination of Benylin's status. *See* Order dated December 8, 1976. This opinion supplements and further explains that order.

Under the terms of the Food, Drug and Cosmetic Act (21 U.S.C. § 301 *et seq.*) a "new drug is one which is not generally recognized among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommneded, or suggested in its label." 21 U.S.C. § 321(p). A new drug may not be sold unless it is the subject of an approved new drug application (NDA), and its sale is limited to the conditions prescribed by the NDA. 21 U.S.C. §§ 353, 355.

In 1948 plaintiff obtained an approved NDA permitting the marketing of Benylin as a prescription drug for the treatment of congestive symptoms related to colds and allergies. The FDA allowed plaintiff to revise the Benylin labeling in 1966 to indicate approval for use as an antitussive (cough suppressant).[1] Prescription sale remained the only approved method of distribution.

The Food, Drug and Cosmetic and regulations promulgated thereunder establish two procedures for obtaining FDA approval of OTC sale of a prescription drug: FDA approval of a supplemental NDA, permitting OTC sale of the drug, may be sought (*see* 21 U.S.C. § 353(b)(1)(c);

[1]The FDA proposed to withdraw this approval in 1972 because the National Academy of Sciences-National Research Council had determined that substantial evidence of Benylin's effectiveness as an antitussive was lacking. 38 Fed. Reg. 4006 (Feb. 9, 1972). Action was deferred pending conclusion of the related OTC drug review. 38 Fed. Reg. 34481 (Dec. 14, 1973).

21 C.F.R. § 310.200) or an OTC review of the drug may be requested (*see* 21 C.F.R. § 330.10).

The OTC drug review procedures were instituted in 1972 to implement a new FDA requirement that a drug must be effective as well as safe. *See* the 1962 Amendments to the Food, Drug, and Cosmetic Act. OTC drugs, already generally recognized as safe, are also tested for effectiveness by the OTC drug review before being approved for continued OTC sale. Similarly, prescription drugs may be examined by the OTC drug review, and if they are found to be generally recognized as safe, effective, and not misbranded, they are approved for OTC sale. As part of the OTC drug review an advisory panel studies a drug and reports its opinion to the Commissioner of Food and Drugs who then makes the final determination of the drug's suitability for OTC sale.

Plaintiff submitted data on Benylin to the OTC Drug Advisory Panel on Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Drugs (CCABA Panel), and in September, 1974, the CCABA Panel tentatively decided to classify diphenhydramine hydrochloride, the active ingredient of Benylin, as generally recognized to be safe and effective for use as an antihistamine and as an antitussive. In November, the CCABA Panel tentatively approved plaintiff's proposed OTC labeling for Benylin Cough Syrup.

In 1974, plaintiff also applied for two supplemental NDA's, one to gain approval for Benylin's use as an antitussive, the other to get permission for the OTC sale of Benylin. The FDA deferred action on these applications pending conclusion of the OTC drug review. Plaintiff was so informed in March, 1975. Letter dated March 11, 1975. Exhibit A to Plaintiff's Complaint.

In February, 1975, plaintiff wrote to the Assistant Director for Implementation Division of OTC Drug Evaluation, proposing to commence OTC sale of Benylin under

the label, Benylin Cough Syrup, as tentatively recommended by the CCABA Panel. Plaintiff wrote, "We will appreciate your approval of this proposal or an administrative indication that such labeling would not cause the product to be subject to regulatory action at this time." Letter dated February 28, 1975. Exhibit B to Plaintiff's Complaint. The FDA gave *de facto* approval to plaintiff's proposal, saying, "Since the new product in question (Benylin Cough Syrup) conforms to the recommendations of the OTC Panel considering this particular type of product and has actually been marketed as a prescription preparation (Benylin Expectorant) for a significant period of time, there would be almost no possibility that we would institute legal action at this time." Letter dated March 16, 1975. Exhibit C to Plaintiff's Complaint. Thereafter, in September, 1975, plaintiff began selling Benylin OTC.

Three months later, in December, 1975, the FDA proposed a new enforcement policy to prevent the OTC sale of prescription drugs until the publication of a final OTC advisory panel approval of the drug for OTC sale. Under the new policy, OTC sale is permitted after publication of the final advisory approval unless the Commissioner indicates his disagreement with the panel recommendation. *See* 40 Fed. Reg. 56675 (Dec. 4, 1975). This policy was made final on August 4, 1976. 41 Fed. Reg. 32580. Although OTC sale of Benylin contravened this new FDA policy, plaintiff continued to sell Benylin OTC throughout most of 1976 without provoking FDA enforcement action.

On September 9, 1976, the CCABA Panel submitted its final recommended approval of OTC sale of Benylin (diphenhydramine hydrochloride) for use as an antitussive. 41 Fed. Reg. 38311, 38340. The Commissioner elected to postpone his statement agreeing or disagreeing with the Panel's recommendation until after the decisions on the still pending applications for supplemental NDA's.

On November 22, 1976, the FDA published a proposed denial of plaintiff's requested supplemental NDA's. 41 Fed. Reg. ____. The Commissioner then issued a proposed monograph dissenting from the CCABA Panel's recommendation. 41 Fed. Reg. ____ (Nov. 22, 1976). Both denial and dissent were based on a conclusion that Benylin's soporific properties make it unsafe for OTC distribution and that there is no substantial evidence of Benylin's effectiveness as an antitussive.

Neither the proposed denial of the supplemental NDA's nor the Commissioner's published dissent to the CCABA Panel recommendation are final decisions. Plaintiff is entitled to a hearing before the denial of the supplemental NDA's becomes final. *See* 21 C.F.R. § 314.200. Similarly, several additional steps, including an oral hearing before the Commissioner of Foods and Drugs, must precede the publication of an OTC drug review final monograph. *See* 21 C.F.R. § 330.10. Despite this absence of a final agency determination of Benylin's status, defendants threatened to institute immediate enforcement action against OTC sale of Benylin in November, 1976. Plaintiff then commenced this action.

The court has jurisdiction over this cause of action pursuant to 28 U.S.C. § 1331(a) (federal question jurisdiction) since the matter in controversy exceeds $10,000 in value and a justiciable controversy between the parties is presented under the Declaratory Judgment Act, 28 U.S.C. § 2201, and under Section 10 of the Administrative Procedure Act (APA), 5 U.S.C. §§ 701-706.[2] Venue is proper in this court since plaintiff is incorporated in the State of Michigan and is thus a resident of the Eastern District of Michigan within the meaning of 28 U.S.C. § 1391(e)(4).

---

[2]There is no need in this case to consider whether *vel non* the APA is an independent grant of jurisdiction since jurisdiction is proper pursuant to 28 U.S.C. § 1331(a); *cf. Hunt* v. *Weinberger*, 572 F. 2d 544 (6th Cir. 1975).

The court must first consider whether judicial review is precluded by the terms of the Administrative Procedure Act. The APA applies to agency action unless there exists another applicable statute which precludes judicial review. 5 U.S.C. § 701(a). No provision of the Food, Drug and Cosmetic Act prohibits judicial review of the FDA's threatened enforcement action. The statute provides for judicial review in the court of appeals of a final FDA decision on plaintiff's applications for the supplemental NDA's. 21 U.S.C. § 355(h). There is likewise a provision for judicial review of a final decision by the OTC drug review. *See* 21 C.F.R. § 330.10(10). However, these sections of the statute are not intended to be exclusive.

> "[A] study of the legislative history [of the Food, Drug and Cosmetic Act] shows rather conclusively that the specific review provisions were designed to give an additional remedy and not to cut down more traditional channels of review."

Abbott Laboratories v. *Gardner*, 387 U.S. 136, 142 (1967).

The APA will not apply to actions committed to agency discretion by law. 5 U.S.C. § 701(b). The actions of the FDA which the court reviews here are discretionary, but that does not render them unreviewable as being committed to agency discretion since the statute does not explicitly give sole discretion to the agency. *See Knight Newspapers, Inc.* v. *United States*, 395 F.2d 353, 358 (6th Cir. 1968); *Sabin* v. *Butz*, 515 F.2d 1061 (10th Cir. 1975). In the evident absence of a clear congressional intent to the contrary, as embodied in the Food, Drug and Cosmetic Act or its legislative history, there should be no restrictions placed on judicial review under the APA. *See Abbott Laboratories* v. *Gardner, supra* at 141. *See also Barlow* v. *Collins*, 397 U.S. 159 (1970). The court concludes that the terms

of the APA do not preclude judicial review in the instant case.

Defendants' threatened enforcement action against OTC sale of plaintiff's product, Benylin, injures plaintiff in fact. Plaintiff is thus a "person aggrieved" with standing to bring this action under the Administrative Procedure Act. 5 U.S.[C.] § 702.

Agency action is reviewable under the Administrative Procedure Act only if it is made reviewable by statute or if it is "final agency action for which there is no other adequate remedy in a court." 5 U.S.C. § 704. Here there has been no final agency determination of Benylin's status; such is not the final agency action now under review. Defendants' threatened enforcement action is agency action (defined by the APA as including administrative sanctions or their equivalent). 5 U.S.C. §§ 701(b)(2), 551(13). It is also a final action since it has a sufficiently direct and immediate effect upon plaintiff. *See United States* v. *Storer Broadcasting Co.*, 351 U.S. 192 (1956); *Abbott Laboratories* v. *Gardner, supra* at 149-153; *Fidelity Television, Inc.* v. *Federal Communications Commission*, 502 F.2d 443 (D.C. Cir. 1974). There is no other adequate remedy provided in the Food, Drug and Cosmetic Act; thus defendants' threatened enforcement action is reviewable under the Administrative Procedure Act.

The court may grant declaratory judgments under either the Administrative Procedure Act or the Declaratory Judgment Act. 5 U.S.C. § 705; 28 U.S.C. § 2201. Plaintiff seeks a declaratory judgment that Benylin is not a new drug and is not limited to distribution by prescription. These issues are currently under consideration by the FDA which has primary jurisdiction over such matters. Since there has been no final agency decision on these issues which is subject to judicial review under the provisions of the Food,

Drug and Cosmetic Act, the court concludes that these issues are not yet ripe for judicial resolution.

> "Without undertaking to survey the intracacies of the ripeness doctrine it is fair to say that its basic rationale is to prevent the courts, through avoidance of premature adjudication, from entangling themselves in abstract disagreements over administrative policies, and also to protect the agencies from judicial interference until an administrative decision has been formalized and its effects felt in a concrete way by the challenging parties. The problem is best seen in a twofold aspect, requiring us to evaluate both the fitness of the issues for judicial decision and the hardship to the parties of withholding court consideration." [footnote omitted]

Abbott Laboratories v. *Gardner*, 387 U.S. 136, 148-149 (1967). *See also The National Ethical Pharmaceutical Assn.* v. *Weinberger*, 503 F.2d 1051 (4th Cir. 1974); *A.O. Smith Corp.* v. *F.T.C.*, 530 F.2d 515 (3rd Cir. 1976); *Bethlehem Steel Corp.* v. *United States Environmental Protection Agency*, 536 F.2d 156 (7th Cir. 1976). There is no hardship to plaintiff in now withholding court consideration of these issues. There will be review of the final decisions under the Food, Drug and Cosmetic Act (*see* discussion, *supra*). Plaintiff's immediate problem is the threatened enforcement action which may be considered more appropriately in the context of plaintiff's request for injunction (*see* discussion, *infra*).

Accordingly, plaintiff's action for a declaratory judgment under the Declaratory Judgment Act and the Administrative Procedure Act may be subject to dismissal.

Alternatively, plaintiff seeks an injunction prohibiting enforcement action against OTC sale of Benylin pending final determination of Benylin's status by the FDA. Injunc-

tive relief is permitted under the terms of the Administrative Procedure Act. 5 U.S.C. § 705. The scope of review under the APA as it applies to this case allows the court to "hold unlawful and set aside agency action, findings, and conclusions found to be arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A).

The court concludes that defendants' threatened immediate enforcement action against the OTC sale of Benylin is arbitrary and capricious. Plaintiff began selling Benylin OTC only after the CCABA Panel gave tentative approval. It began selling Benylin OTC in reliance on FDA assurances that doing so would provoke no FDA regulatory action unless and until the agency made a final decision that Benylin is unsuitable for OTC sale. Although the FDA retracted these assurances three months after plaintiff began selling Benylin OTC, the retraction came too late to affect plaintiff's right to sell. Plaintiff had already made the appropriate changes in Benylin's label and had begun selling it OTC in reliance on the FDA's promise not to institute enforcement proceedings. Under these circumstances it is arbitrary and capricious for the FDA to put plaintiff to the expense and inconvenience of changing its marketing procedures again before a final agency determination on the merits. This is particularly true where, as here, the advisory panel made a thorough study of the drug, its recommendation is supported by the affidavits of several other eminent experts in the field, and, in contrast, the Commissioner's tentative decision not to permit OTC sale is rather incompletely supported. The FDA's threatened regulatory action would be proper if plaintiff had not relied on FDA assurances before beginning OTC sale or if these assurances had been retracted before plaintiff actually began selling Benylin OTC. But in these circumstances the threatened FDA enforcement action is arbitrary and capricious.

Plaintiff seeks relief in equity for defendants' arbitrary and capricious action. Such relief is proper if plaintiff shows that it will suffer irreparable harm unless injunctive relief is granted and that the public interest does not preclude injunctive relief. *Upjohn Co.* v. *Finch,* 303 F. Supp. 241, 261 (W.D. Mich. 1969). The court finds that plaintiff is threatened with irreparable injury. It is asked to recall and relabel its supplies of Benylin, an expensive operation which the final agency decision may render unnecessary. Additionally, if plaintiff does recall and relabel Benylin and then prevails on the merits, it will again have to go through an expensive relabeling process in order to sell Benylin OTC. These expenses will not be recovered. Also the adverse publicity attending either a voluntary recall or a seizure will cause plaintiff incalculable and irreparable harm. The public interest does not here preclude injunctive relief since it is acknowledged by defendants that OTC sale of Benylin represents no imminent hazard to the public health. *See Upjohn Co.* v. *Finch, supra* at 262. The court notes also that Benylin has been sold OTC in Canada for twenty-seven years and in the United States for over a year apparently without creating any hazard.

Defendants contend that the court has no jurisdiction to enjoin the seizures threatened by the FDA. They rely primarily on *Ewing* v. *Mytinger & Casselberry, Inc.,* 339 U.S. 594 (1950), where the United States Supreme Court held that an administrative finding of probable cause to seize certain misbranded drugs was not reviewable except in the libel action itself. Pre-seizure review was held to violate the purpose of the Food, Drug and Cosmetic Act to protect the public through the speedy preventive device of multiple seizures. *See Ewing,* 339 U.S. at 601. *Ewing* may be distinguished. In *Ewing* the plaintiffs sought review of the agency's factual determination of probable cause to seize the misbranded goods. Here the defendants have made

no final factual determination of probable cause. The court has no intention of reviewing any factual issues at this time. Questions of fact such as whether Benylin is still a new drug subject to the conditions of the 1948 NDA, whether it is a new drug entitled to a supplemental NDA permittting OTC sale as an antitussive, or whether it may be sold OTC after an OTC drug review approval, are for the agency to decide. This court requires only that the FDA complete its procedures for making such factual determinations so that a finding of probable cause may be based on a final agency decision. Injunctive relief is proper to accomplish this purpose, and is not precluded by *Ewing*.

Accordingly, the court has entered an order enjoining defendants from instituting enforcement proceedings affecting the distribution of Benylin until thirty days after the FDA makes a final determination of Benylin's status.

JOHN FEIKENS
John Feikens
United States District Judge

DATE: January 7, 1977,
Detroit, Michigan.

APPENDIX C

UNITED STATES COURT OF APPEALS
FOR THE SIXTH CIRCUIT

No. 77-1224

PARKE, DAVIS & COMPANY,
Plaintiff-Appellee,

v.

JOSEPH A. CALIFANO, Secretary of Health, Education and Welfare,
DONALD KENNEDY, Commissioner of Food and Drugs, and the
FOOD AND DRUG ADMINISTRATION,
Defendants-Appellants,

and

UNITED STATES OF AMERICA,
Appellant.

BEFORE: PHILLIPS, Chief Judge; WEICK and LIVELY, Circuit Judges.

JUDGMENT

THIS CAUSE came on to be heard on the record from the United States District Court for the Eastern District of Michigan and was argued by counsel.

ON CONSIDERATION WHEREOF, it is now here ordered and adjudged by this Court that the judgment of the said District Court in this cause be and the same is hereby reversed and the cause remanded for dismissal.

It is further ordered that appellants recover from appellee the costs on appeal, as itemized below, and that execution therefor issue out of said District Court is necessary.

ENTERED BY ORDER OF THE COURT.

JOHN P. HEHMAN
Clerk

[Filed October 26, 1977]

APPENDIX D

UNITED STATES COURT OF APPEALS
FOR THE SIXTH CIRCUIT

No. 77-1224

PARKE, DAVIS & COMPANY,
Plaintiff-Appellee,

v.

JOSEPH A. CALIFANO, Secretary of Health, Education and Welfare,
DONALD KENNEDY, Commissioner of Food and Drugs, and the
FOOD AND DRUG ADMINISTRATION,
Defendants-Appellants,

and

UNITED STATES OF AMERICA,
Appellant.

BEFORE: PHILLIPS, Chief Judge; WEICK and LIVELY, Circuit Judges.

ORDER

Upon consideration of the petition for rehearing filed herein by plaintiff-appellee the court concludes that the issues raised therein were fully considered upon the original submission and decision of this case.

It is therefore ORDERED that the petition for rehearing be and it hereby is denied.

ENTERED BY ORDER OF THE COURT
John P. Hehman, Clerk

By GRACE KELLER
Grace Keller, Deputy Clerk

[Filed November 23, 1977]

APPENDIX E

UNITED STATES COURT OF APPEALS
FOR THE SIXTH CIRCUIT

No. 77-1224

PARKE, DAVIS & COMPANY,
Plaintiff-Appellee,

v.

JOSEPH A. CALIFANO, Secretary of Health, Education and Welfare, *et al.*,
Defendants-Appellants.

BEFORE: PHILLIPS, WEICK and LIVELY, Circuit Judges.

ORDER STAYING MANDATE

ORDERED, that motion to stay mandate herein pending application to the Supreme Court for writ of certiorari is hereby granted and the mandate is stayed for thirty days from this date; provided that, if within such thirty days, the applicant shall file with the Clerk of this Court the certificate of the Clerk of the Supreme Court that the certiorari petition, record, and brief have been filed, the stay shall continue until the final disposition of the case by the Supreme Court. Unless this condition is complied with within such thirty days or any extension thereof made by the Court or any judge thereof, or if the condition is complied with, then upon the filing of copy of an order denying the writ applied for, the mandate shall issue.

ENTERED BY ORDER OF THE COURT.

JOHN P. HEHMAN
Clerk

[Filed December 5, 1977]

APPENDIX F

STATUTES AND REGULATIONS INVOLVED

A. Provisions of the Federal Food, Drug, and Cosmetic Act:

1. Section 201(p) (21 U.S.C. § 321 (p)):

(p) The term "new drug" means—

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

2. Section 503(b) (21 U.S.C. § 353(b)):

(b)(1) A drug intended for use by man which—

(A) is a habit-forming drug to which section 502(d) applies; or

(B) because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug; or

(C) is limited by an approved application under section 505 to use under the professional supervision of a practitioner licensed by law to administer such drug;

shall be dispensed only (i) upon a written prescription of a practitioner licensed by law to administer such drug, or (ii) upon an oral prescription of such practitioner which is reduced promptly to writing and filed by the pharmacist, or (iii) by refilling any such written or oral prescription if such refilling is authorized by the prescriber either in the original prescription or by oral order which is reduced promptly to writing and filed by the pharmacist. The act of dispensing a drug contrary to the provisions of this paragraph shall be deemed to be an act which results in the drug being misbranded while held for sale.

(2) Any drug dispensed by filling or refilling a written or oral prescription of a practitioner licensed by law to administer such drug shall be exempt from the requirements of section 502, except paragraphs (a), (i) (2) and (3), (k), and (l), and the packaging requirements of paragraphs (g), (h), and (p), if the drug bears a label containing the name and address of the dispenser, the serial number and date of the prescription or of its filling, the name of the prescriber, and, if stated in the prescription, the name of the patient, and the directions for use and cautionary statements, if any, contained in such prescription. This exemption shall not apply to any drug dispensed in the course of the conduct of a business

of dispensing drugs pursuant to diagnosis by mail, or to a drug dispensed in violation of paragraph (1) of this subsection.

(3) The Secretary may by regulation remove drugs subject to section 502(d) and section 505 from the requirements of paragraph (1) of this subsection when such requirements are not necessary for the protection of the public health.

(4) A drug which is subject to paragraph (1) of this subsection shall be deemed to be misbranded if at any time prior to dispensing its label fails to bear the statement "Caution: Federal law prohibits dispensing without prescription." A drug to which paragraph (1) of this subsection does not apply shall be deemed to be misbranded if at any time prior to dispensing its label bears the caution statement quoted in the preceding sentence.

(5) Nothing in this subsection shall be construed to relieve any person from any requirement prescribed by or under authority of law with respect to drugs now included or which may hereafter be included within the classifications stated in section 3220 of the Internal Revenue Code (26 U.S.C. 3220), or to marihuana as defined in section 3238(b) of the Internal Revenue Code (26 U.S.C. 3238(b)).

3. Section 505 (21 U.S.C. § 355):

SEC. 505 [355]. (a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) is effective with respect to such drug.

(b) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such persons shall submit to

the Secretary as a part of the application (1) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (2) a full list of the articles used as components of such drug; (3) a full statement of the composition of such drug; (4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (5) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (6) specimens of the labeling proposed to be used for such drug.

(c) Within one hundred and eighty days after the filing of an application under this subsection, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(1) approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) applies, or

(2) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(d) If the Secretary finds, after due notice to the applicant in accordance with subsection (c) and giving him an opportunity for a hearing, in accordance with said

subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e), the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be

concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

(e) The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) that the application contains any untrue statement of a material fact: *Provided*, That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application shall

not be delegated. The Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application with respect to any drug under this section if the Secretary finds (1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (j) or to comply with the notice requirements of section 510(j)(2), or the applicant has refused to permit access to, or copying or verification of, such records as required by paragraph (2) of such subsection; or (2) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of; or (3) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of. Any order under this subsection shall state the findings upon which it is based.

(f) Whenever the Secretary finds that the facts so require, he shall revoke any previous order under subsection (d) or (e) refusing, withdrawing, or suspending approval of an application and shall approve such application or reinstate such approval, as may be appropriate.

(g) Orders of the Secretary issued under this section shall be served (1) in person by any officer or employee of the Department designated by the Secretary or (2) by mailing the order by registered mail or by certified mail addressed to the applicant or respondent at his last-known address in the records of the Secretary.

(h) An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of the court to the Secretary, or any officer designated by him for that purpose, and thereupon the Secretary shall certify and file in the court the record upon which the order complained of was entered, as provided in section 2112 of title 28, United States Code. Upon the filing of such petition such court shall have exclusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do. The finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive. If any person shall apply to the court for leave to adduce additional evidence, and shall show to the satisfaction of the court that such additional evidence is material and that there were reasonable grounds for failure to adduce such evidence in the proceeding before the Secretary, the court may

order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper. The Secretary may modify his findings as to the facts by reason of the additional evidence so taken, and he shall file with the court such modified findings which, if supported by substantial evidence, shall be conclusive, and his recommendation, if any, for the setting aside of the original order. The judgment of the court affirming or setting aside any such order of the Secretary shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of title 28 of the United States Code. The commencement of proceedings under this subsection shall not, unless specifically ordered by the court to the contrary, operate as a stay of the Secretary's order.

(i) The Secretary shall promulgate regulations for exempting from the operation of the foregoing subsections of this section drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs. Such regulations may, within the discretion of the Secretary, among other conditions relating to the protection of the public health, provide for conditioning such exemption upon—

(1) the submission to the Secretary, before any clinical testing of a new drug is undertaken, of reports, by the manufacturer or the sponsor of the investigation of such drug, or preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing;

(2) The manufacturer or the sponsor of the investigation of a new drug proposed to be distributed to investigators for clinical testing obtaining a

signed agreement from each of such investigators that patients to whom the drug is administered will be under his personal supervision, or under the supervision of investigators responsible to him, and that he will not supply such drug to any other investigator, or to clinics, for administration to human beings; and

(3) the establishment and maintenance of such records, and the making of such reports to the Secretary, by the manufacturer or the sponsor of the investigation of such drug, of data (including but not limited to analytical reports by investigators) obtained as the result of such investigational use of such drug, as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug in the event of the filing of an application pursuant to subsection (b).

Such regulations shall provide that such exemption shall be conditioned upon the manufacturer, or the sponsor of the investigation, requiring that experts using such drugs for investigational purposes certify to such manufacturer or sponsor that they will inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, except where they deem it not feasible or, in their professional judgment, contrary to the best interests of such human beings. Nothing in this subsection shall be construed to require any clinical investigator to submit directly to the Secretary reports on the investigational use of drugs.

(j)(1) In the case of any drug for which an approval of an application filed pursuant to this section is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating

to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) of this section: *Provided, however,* That regulations and orders issued under this subsection and under subsection (i) shall have due regard for the professional ethics of the medical profession and the interests of patients and shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by the persons to whom such regulations or orders are applicable, of similar information received or otherwise obtained by the Secretary.

(2) Every person required under this section to maintain records, and every person in charge or custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

B. Provisions of the Administrative Procedure Act:

1. 5 U.S.C. § 702:

§ 702. Right of review

A person suffering legal wrong because of agency action, or adversely affected or aggrieved by agency action within the meaning of a relevant statute, is entitled to judicial review thereof. An action in a court of the United States seeking relief other than money damages and stating a claim that an agency or an officer or employee thereof acted or failed to act in an official capacity or under color of legal authority shall not be

dismissed nor relief therein be denied on the ground that it is against the United States or that the United States is an indispensable party. The United States may be named as a defendant in any such action, and a judgment or decree may be entered against the United States: *Provided,* That any mandatory or injunctive decree shall specify the Federal officer or officers (by name or by title), and their successors in office, personally responsible for compliance. Nothing herein (1) affects other limitations on judicial review or the power or duty of the court to dismiss any action or deny relief on any other appropriate legal or equitable ground; or (2) confers authority to grant relief if any other statute that grants consent to suit expressly or impliedly forbids the relief which is sought.

2. 5 U.S.C. § 704:

§ 704. Actions reviewable

Agency action made reviewable by statute and final agency action for which there is no other adequate remedy in a court are subject to judicial review. A preliminary, procedural, or intermediate agency action or ruling not directly reviewable is subject to review on the review of the final agency action. Except as otherwise expressly required by statute, agency action otherwise final is final for the purposes of this section whether or not there has been presented or determined an application for a declaratory order, for any form of reconsideration, or, unless the agency otherwise requires by rule and provides that the action meanwhile is inoperative, for an appeal to superior agency authority.

3. 5 U.S.C. § 705:

§ 705. Relief pending review

When an agency finds that justice so requires, it may postpone the effective date of action taken by it, pending

judicial review. On such conditions as may be required and to the extent necessary to prevent irreparable injury, the reviewing court, including the court to which a case may be taken on appeal from or on application for certiorari or other writ to a reviewing court, may issue all necessary and appropriate process to postpone the effective date of an agency action or to preserve status or rights pending conclusion of the review proceedings.

4. 5 U.S.C. § 706:

§ 706. Scope of review

To the extent necessary to decision and when presented, the reviewing court shall decide all relevant questions of law, interpret constitutional and statutory provisions, and determine the meaning or applicability of the terms of an agency action. The reviewing court shall—

(1) compel agency action unlawfully withheld or unreasonably delayed; and

(2) hold unlawful and set aside agency action, findings, and conclusions found to be—

(A) arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law;

(B) contary to constitutional right, power, privilege, or immunity;

(C) in excess of statutory jurisdiction, authority, or limitations, or short of statutory right;

(D) without observance of procedure required by law;

(E) unsupported by substantial evidence in a case subject to sections 556 and 557 of this title or otherwise reviewed on the record of an agency hearing provided by statute; or

(F) unwarranted by the facts to the extent that the facts are subject to trial de novo by the reviewing court.

In making the foregoing determinations, the court shall review the whole record or those parts of it cited by a party, and due account shall be taken of the rule of prejudicial error.

C. Regulations

1. Procedures for Classification of Over-the-Counter Drugs, 37 Fed. Reg. 9464 (May 11, 1972) (pertinent portions):

SUBCHAPTER C—DRUGS

PART 130—NEW DRUGS

Procedures for Classification of Over-the-Counter Drugs

A notice of proposed rule making regarding these regulations was published in the FEDERAL REGISTER of January 5, 1972 (37 F.R. 85). Interested persons were invited to submit comments on the proposal within 60 days. Forty-three comments were received. The comments concerned almost every part of the proposal and its accompanying preamble.

GENERAL COMMENTS

1. The preamble to the proposal stated that the review of prescription drugs was being completed and that it was now appropriate to conduct a similar review of OTC drugs. Most of the comments agreed that OTC drugs must be safe and effective and properly labeled so that the consuming public is protected. In addition, most comments supported the class approach to the review of

OTC drugs provided such a review is scientifically sound. The Food and Drug Administration believes that the therapeutic category approach to OTC drugs is appropriate, since there are only an estimated 200 active ingredients in the thousands of OTC drugs now marketed; therefore, this approach is adopted in the final regulations.

* * *

9. The Commissioner, in the preamble to the proposal, set forth seven paragraphs indicating the reasons why the agency proposed to adopt the OTC therapeutic category review approach. A number of comments argued that the Food and Drug Administration's justifications for this approach (lack of funds, lack of manpower, and competitive unfairness between drugs if a drug-by-drug approach was adopted) were insufficient justifications. It was stated that the lack of manpower and funds were not sufficient justifications because they could be cured by seeking additional appropriations and that the idea of competitive unfairness between manufacturers makes a shambles of the law. The Food and Drug Administration believes that its resources of manpower and funds are properly considered in deciding how best to approach its consumer protection activities. Based on present resources it would not be possible to adopt a drug-by-drug approach even if it were a better method. The Commissioner has also concluded that a drug-by-drug approach is not the best method of proceeding, since it would be so cumbersome, time consuming, and confusing. By adopting these regulations there will be no question as to which drugs are generally recognized as safe and effective and not misbranded, and what labeling is permitted.

* * *

24. One comment questioned whether the agency intends to require manufacturers of OTC products that were covered by an NDA to submit the NDA data for review by the OTC panels. The Food and Drug Administration intends that the review will cover all OTC drugs, including those with approved NDA's since 1962. NDA files will therefore be a part of the information included in the review. If a final monograph includes an OTC drug which is covered by an NDA as generally recognized as safe and effective, the drug will be removed from NDA status. A finding by a panel that an OTC drug covered by an NDA is not generally recognized as safe and effective may or may not affect the NDA, depending upon the applicability of the basis for the decision. If such action does affect an NDA, it will be handled through the usual new drug procedures.

* * *

COMMENTS RELATING TO SPECIFIC PROVISIONS OF PROPOSED § 130.301 (21 CFR 130.301)

I, PARAGRAPH (a)(1) ADVISORY REVIEW PANELS

26. There were numerous comments that the advisory panels should have "expertise" in OTC drugs. The Commissioner in his appointments is choosing as panel members individuals recommended by organizations representing professional, consumer, and industry interests, in addition to those recommended by his own staff. The individuals selected for panel membership are leading experts in the therapeutic category that the panel is reviewing. It has also been suggested that the panel include a general practitioner as one of the members so that the panels are not made up completely of individuals from teaching institutions. There is no exclusion of the general practitioner since any qualified person can be a panel member, and an attempt will be made to have

such practitioners represented on as many panels as possible. Many of the panel members will no doubt have a private practice, and whether or not a panel member is a general practitioner will have no bearing on whether or not he is qualified. The only two conditions for panel membership are that the individual have expertise in the therapeutic category under consideration and that he not have a conflict of interest.

* * *

71. It was also noted in comments that the panel's recommendation may result in moving a drug which is on prescription status to OTC status. Although the data submitted by interested parties are to relate only to OTC drugs, the panel is charged with making recommendations with respect to all drugs that should be on OTC status. Any interested person may, of course, submit data and views suggesting that a prescription drug be moved to OTC status.

* * *

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040-42 as amended, 1050-53 as amended, 1055-56 as amended by 70 Stat. 919 and 72 Stat. 948; 21 U.S.C. 321, 352, 355, 371) and the Administrative Procedure Act (secs. 4, 10, 60 Stat. 238 and 243 as amended; 5 U.S.C. 553, 702, 703, 704) and under authority delegated to the Commissioner (21 CFR 2.120), Part 130 is amended by adding a new Subpart D consisting at this time of one section, as follows:

Subpart D—Over-the-Counter Drugs Which Are Generally Recognized as Safe and Effective and Not Misbranded

§ 130.301 Over-the-counter (OTC) drugs for human use; procedures for rule making for the classification of OTC drugs as generally recognized as safe and effective and not misbranded under prescribed, recommended, or suggested conditions of use.

For purposes of classifying over-the-counter (OTC) drugs as drugs generally recognized among qualified experts as safe and effective for use and as not misbranded drugs, the following regulations shall apply:

(a) *Procedure for establishing OTC drug monographs*—(1) *Advisory review panels.* The Commissioner shall appoint advisory review panels of qualified experts to evaluate the safety and effectiveness of OTC drugs, to review OTC drug labeling, and to advise him on the promulgation of monographs establishing conditions under which OTC drugs are generally recognized as safe and effective and not misbranded. A single advisory review panel shall be established for each designated category of OTC drugs and every OTC drug category will be considered by a panel. The members of a panel shall be qualified experts (appointed by the Commissioner) and may include persons from lists submitted by organizations representing professional, consumer, and industry interests. The Commissioner shall designate the chairman of each panel. Summary minutes of all meetings shall be made.

(2) *Request for data and views.* The Commissioner will publish a notice in the FEDERAL REGISTER requesting interested persons to submit, for review and evaluation by an advisory review panel, published and unpublished data and information pertinent to a designated category of OTC drugs. Data and information submitted pursuant

to a published notice, and falling within the confidentiality provisions of 18 U.S.C. 1905, 5 U.S.C. 552(b), or 21 U.S.C. 331(j), shall be handled by the advisory review panel and the Food and Drug Administration as confidential until publication of a proposed monograph and the full report(s) of the panel.

* * *

(3) *Deliberations of an advisory review panel.* An advisory review panel will meet as often and for as long as is appropriate to review the data submitted to it and to prepare a report containing its conclusions and recommendations to the Commissioner with respect to the safety and effectiveness of the drugs in a designated category of OTC drugs.

* * *

(5) *Advisory review panel report to the Commissioner.* An advisory review panel shall submit to the Commissioner a report containing its conclusions and recommendations with respect to the conditions under which OTC drugs falling within the category covered by the panel are generally recognized as safe and effective and not misbranded. Included within this report shall be:

(i) A recommended monograph or monographs covering the category of OTC drugs and establishing conditions under which the drugs involved are generally recognized as safe and effective and not misbranded. This monograph may include any conditions relating to active ingredients, labeling indications, warnings and adequate directions for use, prescription of OTC status, and any other conditions necessary and appropriate for the safety and effectiveness of drugs covered by the monograph.

* * *

(6) *Proposed monograph.* After reviewing the conclusions and recommendations of the advisory review panel, the Commissioner shall publish in the FEDERAL REGISTER a proposed order containing:

(i) A monograph or monographs establishing conditions under which a category of OTC drugs is generally recognized as safe and effective and not misbranded.

(ii) A statement of the conditions excluded from the monograph on the basis of the Commissioner's determination that they would result in the drug's not being generally recognized as safe and effective or would result in misbranding.

(iii) A statement of the conditions excluded from the monograph on the basis of the Commissioner's determination that the available data are insufficient to classify such conditions under either subdivision (i) or (ii) of this subparagraph.

(iv) The full report(s) of the panel to the Commissioner.

The proposed order shall specify a reasonable period of time within which conditions falling within subdivision (iii) of this subparagraph may be continued in marketed products while the data necessary to support them are being obtained for evaluation by the Food and Drug Administration. The summary minutes of the panel meetings shall be made available to interested persons upon request. Any interested person may, within 60 days after publication of the proposed order in the FEDERAL REGISTER, file with the Hearing Clerk of the Food and Drug Administration written comments in quintuplicate. Comments may be accompanied by a memorandum or brief in support thereof. All comments may be reviewed at the office of the Hearing Clerk during regular working hours, Monday through Friday. Within 30 days after the final day for submission of comments, reply comments

may be filed with the Hearing Clerk; these comments shall be utilized to reply to comments made by other interested persons and not to reiterate a position.

(7) *Tentative final monograph.* After reviewing all comments and reply comments, the Commissioner shall publish in the FEDERAL REGISTER a tentative order containing a monograph establishing conditions under which a category of OTC drugs is generally recognized as safe and effective and not misbranded. Within 30 days, any interested party may file with the Hearing Clerk of the Food and Drug Administration written objections specifying with particularity the omissions or additions requested. These objections are to be supported by a brief statement of the grounds therefor. A request for an oral hearing may accompany such objections.

(8) *Oral hearing before the Commissioner.* After reviewing objections filed in response to the tentative filed monograph, the Commissioner, if he finds reasonable grounds in support thereof, shall by notice in the FEDERAL REGISTER schedule an oral hearing. The notice scheduling an oral hearing shall specify the length of the hearing and how the time shall be divided among the parties requesting the hearing. The hearing shall be conducted by the Commissioner and may not be delegated.

(9) *Final monograph.* After reviewing the objections and considering the arguments made at any oral hearing, the Commissioner shall publish in the FEDERAL REGISTER a final order containing a monograph establishing conditions under which a category of OTC drugs is generally recognized as safe and effective and not misbranded. The monograph shall become effective as specified in the order.

* * *

Effective date. This order shall become effective 60 days after its date of publication in the FEDERAL

REGISTER, except as to any provisions that may be stayed by the filing of proper objections. Notice of the filing of objections or lack therof will be given by publication in the FEDERAL REGISTER.

Dated: May 8, 1972

CHARLES C. EDWARDS,
Commissioner of Food and Drugs.

2. Marketing Status of Ingredients Recommended for Over-the-Counter Use, 41 Fed. Reg. 32580 (August 4, 1976) (pertinent portions):

SUBCHAPTER D—DRUGS FOR HUMAN USE

(Docket No. 75N—0345)

PART 310—NEW DRUGS

PART 330—OVER-THE-COUNTER (OTC) HUMAN DRUGS GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED

Marketing Status of Ingredients Recommended for Over-the-Counter Use

The Food and Drug Administration (FDA) is amending the regulations to clarify the marketing status of ingredients recommended for OTC (over-the-counter) use, effective September 3, 1976.

In the FEDERAL REGISTER of December 4, 1975 (40 FR 56675), the Commissioner of Food and Drugs proposed to amend Part 310 (21 CFR Part 310) to clarify that the OTC drug review process is another procedure for transferring an ingredient from prescription to OTC status and Part 330 (21 CFR Part 330) to set forth FDA policy regarding the marketing of OTC drug products containing an active ingredient (a) that is at a dosage level higher than that currently available in an OTC drug product, or (b) that is currently limited to prescription use, but that is regarded by an OTC drug advisory review panel as suitable for OTC use. Interested persons were invited to submit comments on the proposal by February 2, 1976.

The Commissioner is now issuing a final regulation setting forth the following policies:

1. Any OTC drug product containing an active ingredient previously limited to prescription use for the indication and route of administrative under consideration by an OTC drug advisory review panel, or containing any active ingredient at a dosage level higher than that available in an OTC drug product on December 4, 1975, which ingredient and/or dosage level is classified by a panel in category I (generally recognized as safe and effective and not misbranded), shall be considered a new drug if marketed before the date of publication in the FEDERAL REGISTER of a proposed monograph for the ingredient.

2. Any such drug product may be marketed after the date of publication of a proposed monograph in the FEDERAL REGISTER, but before the effective date of a final monograph, subject to the risk that the Commissioner may not accept a panel's recommendation but adopt a different position that could require relabeling, recall, or other regulatory action.

* * *

These policies reflect current FDA enforcement policies, and the regulations embodying them are therefore effective immediately.

* * *

The Commissioner will ordinarily announce his tentative decision not to accept a panel's recommendation regarding specific ingredients or dosage levels of ingredients proposed for classification in category I at the time the proposed monograph is published in the FEDERAL REGISTER. This announcement will be included in the preamble to the proposed monograph or in a separate notice in the FEDERAL REGISTER. In some instances, the Commissioner may not announce his decision not to

accept a panel's recommendation until after the date of publication of the proposed monograph, as stated in § 330.13(b)(2) (21 CFR 330.13(b)(2)). The wording of paragraph (b)(2) has been revised to clarify this. In either case, his decision will be fully documented in the administrative record. The Commissioner emphasizes, however, that his tentative decision not to accept a panel's recommendation does not mean that he may not subsequently agree with the panel when a final monograph is published. In any event, persons marketing a drug product not in compliance with the Commissioner's tentative decision not to accept a panel's recommendation will be subject to regulatory action and the Commissioner's determination will therefore effectively be reviewable in the context of any proceeding brought by FDA pursuant to this policy.

* * *

In the preamble to the December 4 proposal, the Commissioner described the two procedures by which a prescription drug ingredient may lawfully be marketed for OTC use. Ingredients limited to prescription use under section 503(b)(1)(C) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 353(b)(1)(C)) may acquire OTC status by a petition submitted pursuant to the procedures set forth in § 310.200 (21 CFR 310.200); the OTC drug review process provides another procedure.

The Commissioner notes that OTC drug advisory review panels were directed to review and make recommendations concerning OTC drug ingredients as well as certain prescription drug ingredients that could be used safely and effectively by laymen. Several panels have made such recommendations regarding prescription drug ingredients. It is, however, impractical and it was never intended that these panels evaluate all prescription drug ingredients within the therapeutic category under their review. The Commissioner advises that any interested

person may, as the comment indicated, submit data and views to a panel suggesting that a prescription drug be moved to OTC status. Any interested person may also file a petition with FDA requesting a change from prescription to OTC status for a specific drug product.

* * *

7. The Commissioner points out that the ingredients diphenhydramine, oxymetazoline, and chlorpheniramine, which were cited in the December 4 proposal, will be dealt with in the proposed monograph for OTC cold, cough, allergy, bronchodilator, and antiasthmatic products to be published in a future issue of the FEDERAL REGISTER.

Therefore, under the Federal Food, Drug and Cosmetic Act (secs. 502, 505, 701(a), 52 Stat. 1050-1053, as amended, 1055 (21 U.S.C. 352, 355, 371(a)) and under authority delegated to the Commissioner (21 CFR 5.1) (recodification published in the FEDERAL REGISTER of June 15, 1976 (41 FR 24262)), Chapter I of Title 21 of the Code of Federal Regulations is amended as follows:

1. In Part 310, § 310.200 is amended by revising paragraphs (a) and (c) and adding new paragraph (e) to read as follows:

§ 310.200 Prescription-exemption procedure.

(a) *Duration of prescription requirement.* Any drug limited to prescription use under section 503(b)(1)(C) of the act remains so limited until it is exempted as provided in paragraph (b) or (e) of this section.

* * * * *

(c) *New drug status of drugs exempted from the prescription requirement.* A drug exempted from the prescription requirement under the provisions of paragraph (b) of this section is a "new drug" within the

meaning of section 201(p) of the act until it has been used to a material extent and for a material time under such conditions except as provided in paragraph (e) of this section.

* * * * *

(e) *Prescription-exemption procedure of OTC drug review.* A drug limited to prescription use under section 503(b)(1)(C) of the act may also be exempted from prescription-dispensing requirements by the procedure set forth in § 330.13 of this chapter.

---

2. In Part 330, a new § 330.13 is added to read as follows:

§ 330.13 Conditions for marketing ingredients recommended for over-the-counter (OTC) use under the OTC drug review.

(a) Before the publication in the FEDERAL REGISTER of an applicable proposed monograph, an OTC drug product that contains: (1) An active ingredient limited, on or after May 11, 1972, to prescription use for the indication and route of administration under consideration by an OTC advisory review panel, and not thereafter exempted from such limitation pursuant to § 310.200 of this chapter, or

(2) An active ingredient at a dosage level higher than that available in an OTC drug product on December 4, 1975, shall be regarded as a new drug within the meaning of section 201(p) of the act for which an approved new drug application is required.

(b) (1) An OTC drug product that contains: (i) An active ingredient limited, on or after May 11, 1972, to prescription use for the indication and route of administration under consideration by an OTC advisory review panel, and not thereafter exempted from such limitation pursuant to § 310.200 of this chapter, or

(ii) An active ingredient at a dosage level higher than that available in an OTC drug product on December 4, 1975, which ingredient and/or dosage level is classified by the panel in category I (conditions subject to § 330.10(a)(6)(i)) shall be regarded as a new drug within the meaning of section 201(p) of the act for which an approved new drug application is required if marketed for OTC use prior to the date of publication in the FEDERAL REGISTER of a proposed monograph.

(2) An OTC drug product covered by paragraph (b)(1) of this section which is marketed after the date of publication in the FEDERAL REGISTER of a proposed monograph but prior to the effective date of a final monograph shall be subject to the risk that the Commissioner may not accept the panel's recommendation and may instead adopt a different position that may require relabeling, recall, or other regulatory action. The Commissioner may state such position at any time by notice in the FEDERAL REGISTER, either separately or as part of another document; appropriate regulatory action will commence immediately and will not await publication of a final monograph. Marketing of such a product with a formulation or labeling not in accord with a proposed monograph or tentative final monograph also may result in regulatory action against the product, the marketer, or both.

(c) An OTC drug product that contains: (1) An active ingredient limited, on or after May 11, 1972, to prescription use for the indication and route of administration under consideration by an OTC advisory review panel, and not thereafter exempted from such limitation pursuant to § 310.200 of this chapter, or

(2) An active ingredient at a dosage level higher than that available in any OTC drug product on

December 4, 1975, which ingredient and/or dosage level is classified by the panel in category II (conditions subject to § 330.10(a)(6)(ii)), shall be regarded as a new drug within the meaning of section 201(p) of the act for which an approved new drug application is required for marketing.

(d) An OTC drug product that contains: (1) An active ingredient limited, on or after May 11, 1972, to prescription use for the indication and route of administration under consideration by an OTC advisory review panel, and not thereafter exempted from such limitation pursuant to § 310.200 of this chapter, or

(2) An active ingredient at a dosage level higher than that available in any OTC drug product on December 4, 1975 which ingredient and/or dosage level is classified by the panel in category III (conditions subject to § 330.10(a)(6)(iii)), may be lawfully marketed only after either the ingredient is determined by the Commissioner to be generally recognized as safe and effective, or a new drug application for the product has been approved.

Effective date: This regulation shall become effective on September 3, 1976.

(Secs. 502, 505, 701(a), 52 Stat. 1050-1053, as amended, 1055 (21 U.S.C. 352, 355, 371(a)))

Dated: July 26, 1976.

SHERWIN GARDNER,
Deputy Commissioner of
Food and Drugs.

3. Establishment of a Monograph for OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products, 41 Fed. Reg. 38312 (September 9, 1976) (pertinent portions):

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 341]

[Docket No. 76N-0052]

OVER-THE-COUNTER DRUGS

Establishment of a Monograph for OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products

The Food and Drug Administration (FDA) proposes to establish conditions under which over-the-counter (OTC) cold, cough, allergy, bronchodilator and antiasthmatic drugs are generally recognized as safe and effective and not misbranded, based on the recommendations of the Advisory Review Panel on Over-The-Counter (OTC) Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products; comments by December 8, 1976.

Pursuant to Part 330 (21 CFR Part 330), the Commissioner of Food and Drugs received on March 3, 1976, the report of the Advisory Review Panel on Over-The-Counter (OTC) Cold, Cough, Allergy Bronchodilator and Antiasthmatic Products. In accordance with § 330.10(a)(6), (21 CFR 330.10(a)(6)), the Commissioner is issuing (1) a proposed regulation containing the monograph recommended by the Panel establishing conditions under which OTC cold, cough, allergy, bronchodilator and antiasthmatic drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel that they would result in the drugs not being generally

recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel that the available data are insufficient to classify such conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel to the Commissioner. The summary minutes of the Panel meetings are on public display in the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852.

The purpose of issuing the unaltered conclusions and recommendations of the Panel is to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The Commissioner has not yet fully evaluated the report, but has concluded that it should first be issued as a formal proposal to obtain full public comment before any decision is made on the recommendations of the Panel. The report of the Panel represents the best scientific judgment of the members. The report has been prepared independently of FDA and does not necessarily reflect the agency position on any particular matter contained therein. After a careful review of all comments submitted in response to this proposal, the Commissioner will issue a tentative final regulation in the FEDERAL REGISTER to establish a monograph for OTC cold, cough, allergy, bronchodilator and antiasthmatic drug products.

In accordance with § 330.10(a)(2) (21 CFR 330.10(a)(2)), all data and information concerning OTC cold, cough, allergy, bronchodilator and antiasthmatic drug products submitted for consideration by the Advisory Review Panel have been handled as confidential by the Panel and FDA. All such data and information shall be put on public display at the office of the Hearing Clerk, Food and Drug Administration, on or before October 12, 1976, except to the extent that the person

submitting it demonstrates that it still falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality shall be submitted to FDA, Bureau of Drugs, Division of OTC Drug Products Evaluation (HFD—510), 5600 Fishers Lane, Rockville, MD 20852.

Based upon the conclusions and recommendations of the Panel, the Commissioner proposes, upon publication of the final regulation:

1. That the conditions included in the monograph on the basis of the Panel's determination that they are generally recognized as safe and effective and are not misbranded (Category I) be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

2. That the conditions excluded from the monograph on the basis of the Panel's determination that they would result in the drug not being generally recognized as safe and effective or would result in misbranding (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER, regardless whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient (Catagory III) to classify such conditions either as Category I—generally recognized as safe and effective and not misbranded, or as Category II— not being generally recognized as safe and effective or would result in misbranding, be permitted to remain in use for not longer than 2 to 5 years (for the specific conditions specified in this document) after the date of publication of the final monograph in the FEDERAL REGISTER, if the manufacturer or distributor of

any such drug utilizing such conditions in the interim conducts tests and studies adequate and appropriate to satisfy the questions raised with respect to the particular condition by the Panel. The period of time within which studies must be completed will be carefully reviewed by the Commissioner after receipt of comments on this document and will probably be revised downward.

This proposal sets forth the conclusion of the Advisory Review Panel on Over-the-Counter (OTC) Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products that several ingredients are safe and effective for OTC use which heretofore have been limited to prescription use or classified for OTC use at a dosage level lower than that recommended by the Panel. The Commissioner is aware that a number of questions have been presented to the agency regarding the OTC marketing status of ingredients or amounts of ingredients previously limited to prescription use prior to finalization of an applicable monograph for the ingredients. The reclassification of ingredients from prescription to OTC status presents important issues that need careful and special consideration.

Accordingly, the Commissioner proposed, in the FEDERAL REGISTER of December 4, 1975 (40 FR 56675), a policy to clarify the marketing status of (1) all ingredients currently restricted to prescription use which an OTC advisory panel recommends as Category I (safe and effective), Category II (not safe and effective), or Category III (the available data are insufficient to classify the drug); and (2) the use of active ingredients at dosage levels higher than that available in any OTC drug product.

The Commissioner also advised in the preamble to the proposal in the December 4, 1975 FEDERAL REGISTER that he may indicate his disagreement with the panel's recommendation(s) regarding specific ingredients pro-

posed for Category I, e.g., ingredients having manufacturing or formulation problems or unresolved questions concerning a potential for abuse or misuse; and he may make a tentative determination that an approved new drug application (NDA) is required for marketing an OTC product containing such ingredients. The Commissioner acted on this proposal by final regulation published in the FEDERAL REGISTER of August 4, 1976 (41 FR 32580).

The Commissioner has reviewed those ingredients included in the Panel's recommendations that are currently limited to prescription use or classified for OTC use at a dosage level lower than that recommended by the Panel. He has made an initial determination that an approved NDA is required for OTC marketing of promethazine for any indication, for OTC marketing of doxylamine succinate as an antihistamine at a dosage level in excess of 7.5 milligrams (mg), and for OTC marketing of diphenhydramine as an antihistamine. The Commissioner is deferring his decision on the Panel's recommendation that diphenhydramine be considered generally recognized as safe and effective for OTC use as an antitussive until the agency has had an opportunity to rule on a supplemental NDA now pending for OTC use of an antitussive product containing diphenhydramine. The Commissioner has made an initial determination to accept the Panel's recommendations on OTC use of a number of ingredients among which are chlorpheniramine, pseudoephedrine, theophylline, and methoxyphenamine. However, the Commissioner wishes to raise several pertinent points regarding these drugs, and they are fully explained below.

* * *

Diphenhydramine hydrochloride. Diphenhydramine hydrochloride is the active ingredient in several products with approved NDA's. All such products are limited to

prescription use. The Panel recommended that diphenhydramine hydrochloride be classified in Category I for antihistaminic use at 25 to 50 mg, which is the usual prescription dosage level. Diphenhydramine hydrochloride, like doxylamine succinate, is a member of the ethanolamine class of antihistamines. It, too, has a pronounced tendency to produce sedation in a high proportion of those persons who take it (*AMA Drug Evalulation*, 2d Ed., p. 493). For this reason, the Commissioner concludes that diphenhydramine hydrochloride should remain a prescription new drug ingredient and not be available for use as an OTC antihistamine. No diphenhydramine hydrochloride product is currently marketed OTC as an antihistamine at any dosage level.

The Panel also recommended that diphenhydramine hydrochloride be classified in Category I for OTC use as an antitussive. Diphenhydramine hydrochloride is the active ingredient in a cough syrup product now being marketed OTC. The currently effective NDA for this product limits it to prescription use and labels it as an expectorant only. The holder of the NDA has submitted a supplemental NDA that contains data in support of a claim that the product is safe and effective for use as an antitussive. The supplemental NDA also requests that the product be approved for OTC use. The Commissioner has concluded that the marketing status of diphenhydramine hydrochloride as an antitussive should be resolved by first considering the approvability of this supplemental NDA. After that, he will address the Panel's recommendation that diphenhydramine hydrochloride be considered generally recognized as safe and effective for OTC use as an antitussive.

The agency will rule on the pending supplemental NDA in the near future. The Commissioner advises that if the supplemental NDA is denied because diphenhydramine hydrochloride in the amount present in that product is not considered safe and effective for OTC use as an antitussive, he will at that time issue a notice in the FEDERAL REGISTER stating his disagreement with the Panel's recommendation that diphenhydramine hydrochloride be classified in Category I for OTC antitussive use. In that event, any such product marketed OTC would thereupon be subject to immediate regulatory action, in accordance with enforcement policy announced in the FEDERAL REGISTER of August 4, 1976 (41 FR 32580). If the supplemental NDA is approved, the Commissioner may nevertheless conclude that the safety and/or effectiveness of antitussive products containing diphenhydramine hydrochloride has not achieved general recognition in the scientific community, and he may state such conclusion by notice in the FEDERAL REGISTER when the supplemental NDA is approved or at a later time, e.g., in the preample to the tentative final monogaph.

The Commissioner notes that the marketing status of diphenhydramine hydrochloride as an antihistamine raises different issues from those surrounding its OTC use as an antitussive. The indications, dosage levels, and number of available effective alternatives are different depending on the condition for which diphenhydramine hydrochloride is to be used. Also, the effectiveness of the ingredient is established in relation to antihistaminic use, but has not yet been ruled on in the context of the pending supplemental NDA for OTC use of a cough syrup product. Accordingly, the Commissioner's initial decision not to accept the Panel's recommendation for Category I classification of diphenhydramine hydrochloride for use as an antihistamine is independent of his decision on its status as an antitussive, although, obviously, some of the underlying factual considerations are common to each.

* * *

The conclusions and recommendations in the report of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products follow:

In the FEDERAL REGISTER of January 5, 1972 (37 FR 85), the Commissioner of Food and Drugs announced a proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels. On May 8, 1972, the Commissioner signed the final regulations providing for the OTC drug review under § 330.10 published in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464), which were made effective immediately. Pursuant to these regulations the Commissioner issued a request for data and information on all cold, cough, allergy, bronchodilator and antiasthmatic (CCABA) active ingredients in drug products, in the FEDERAL REGISTER of August 9, 1972 (37 FR 16029).

The Commissioner appointed the following Panel to review the data and information submitted and to prepare a report on the safety, effectiveness, and labeling of OTC cold, cough, allergy, bronchodilator and antiasthmatic ingredients pursuant to § 330.10(a)(1):

Francis C. Lowell, M.D., Chairman
Hylan A. Bickerman, M.D.
Halia Brown, M.D.
Robert K. Chalmers, Ph.D.
Mary Jo Reilly, M.S.
James R. Tureman, M.D.
Colin R. Woolf, M.D.

The Panel was first convened on November 6, 1972, in an organizational meeting. Working meetings were held on December 11 and 12, 1972; January 23 and 24, February 28 and March 1, April 5 and 6, May 10 and 11, June 19 and 20, September 25 and 26, October 31 and November 1, December 6 and 7, 1973; January 8 and 9, March 19 and 20, June 12 and 13, September 11

and 12, October 31, November 1, December 3 and 4, 1974; January 30 and 31, April 3, 4 and 5, May 15 and 16, July 17 and 18, September 24 and 25, November 19, 20 and 21, and December 17, 18 and 19, 1975; February 2, and March 2 and 3, 1976.

Two nonvoting liaison representatives served on the Panel. Mrs. Anita Ohlhausen, nominated by an ad hoc group of consumer organizations, served as the consumer liaison and Joseph L. Kanig, Ph.D., nominated by the Proprietary Association, served as the industry liaison. The following employees of the Food and Drug Administration served: Anna L. Standard, M.D., Executive Secretary until March 26, 1974 followed by Joel Aronson, R. Ph.; Thomas D. DeCiliis, R. Ph., Panel Administrator; Recie Bomar, R. Ph., Drug Information Analyst until February, 1973 followed by Lloyd G. Scott, R. Ph. until May, 1974 followed by Gary P. Trosclair, R. Ph.

In addition to the Panel members and liaison representatives, the following individuals were given an opportunity to appear before the panel to express their views either at their own or at the Panel's request:

Paul Bass, Ph.D.
C. Warren Bearman, M.D.
John Behrman, M.D.
Richard C. Brogle, Ph.D.
C. Edward Buckley III, M.D.
A. Lee Caldwell, Jr., Ph.D.
Robert B. Choate
Sanford Chodosh, M.D.
John T. Connell, M.D.
Joseph Dresner
Constantine Falliers, M.D.
Arthur D. Flanagan, M.D.
Spencer Free, Ph.D.
Arthur Grollman, M.D.
Robert M. Hodges

George F. Hoffnagle, Sc.D.
Clarence Imboden, M.D.
Charles Janeway, M.D.
Anita Johnson, Esq.
Stuart J. Land, Esq.
Ben Marr Lanman, M.D.
Vincent D. Larkin, M.D.
Louie G. Linarelli, M.D.
Jennifer Loggie, M.D.
S. J. London, M.D.
Leslie M. Lueck, M.D.
Guillermo Martinez
John McLean, M.D.
Fletcher B. Owen, M.D.
Elias W. Packman, Sc.D.
Joseph Page, Esq.
Joseph J. Pittelli, M.D.
William R. Pool
Thomas W. Richards, M.D.
Norman Salik, M.D.
Robert T. Scanlon, M.D.
Daniel L. Shaw, Jr., M.D.
Alex Silverglade, M.D.
Joseph Smith, M.D.
Alfred E. Sutherland, Esq.
Garret W. Swenson, Esq.
M. L. Thomson, M.D.
Sumner Yaffee, M.D.

No person who so requested was denied an opportunity to appear before the Panel.

The Panel has thoroughly reviewed the literature, and the various data submissions, has listened to additional testimony from interested parties and has considered all pertinent data and information submitted through March 3, 1976 in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel's findings with respect to these classes of drugs are set out in three categories:

Category I. Conditions under which cold, cough, allergy, bronchodilator and antiasthmatic products are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which cold, cough, allergy, bronchodilator and antiasthmatic products are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

The Panel recommends the following for each group of drugs:

1. That the conditions included in the monograph on the basis of the Panel's determination that they are generally recognized as safe and effective and are not misbranded (Category I) be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

2. That the conditions excluded from the monograph on the basis of the Panel's determination that they would result in the drug not being generally recognized as safe and effective or would result in misbranding (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER, regardless of whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient (Category III) to classify such conditions either as Category I—generally recog-

nized as safe and effective and not misbranded; or as Category II—not being generally recognized as safe and effective or would result in misbranding, be permitted to remain in use for a period of time justified in the report of 2, 3, 4 or 5 years for the specific conditions after the date of publication of the final monograph in the FEDERAL REGISTER, if the manufacturer or distributor of any such drug utilizing such conditions in the interim conducts tests and studies adequate and appropriate to satisfy the questions raised with respect to the particular condition by the Panel.

I. SUBMISSION OF DATA AND INFORMATION

Pursuant to the notice published in the FEDERAL REGISTER of August 9, 1972 (37 FR 16029) requesting the submission of data information on cold, cough, allergy, bronchodilator and antiasthmatic (CCABA) drugs, the following firms made submissions relating to the indicated products:

A. SUBMISSIONS BY FIRMS

Firm	*Marketed products*
* * *	
Parke-Davis & Co., Detroit, Mich. 48232	Benylin Cough Syrup, Benadryl.
* * *	

II. GENERAL STATEMENTS AND RECOMMENDATIONS

A. GENERAL COMMENT

The OTC cold, cough, allergy, bronchodilator and antiasthmatic Panel was charged with the review and the evaluation of safety and effectiveness data on cold, cough, allergy, bronchodilator, and antiasthmatic ingredients and combinations thereof, the adequacy of their labeling, and to advise the Commissioner of Food and Drugs on the promulgation of monographs establishing conditions under which these over-the-counter (OTC)

drug products are generally recognized as safe and effective and not misbranded. The Panel also served as a forum for the exchange of views regarding the prescription or nonprescription status of these various active ingredients and combinations thereof. Panel members were expected to call upon their own expert knowledge and experience in carrying out each element of this charge. Specifically the Panel was charged with the following:

1. Review and evaluation of all data made available to the panel members concerning the safety and effectiveness of cold, cough, allergy, bronchodilator and antiasthmatic treatment and prevention agents, and combinations thereof, utilized in these OTC drug products.

2. Advising the Food and Drug Administration as to the adequacy of the labeling of such cold, cough, allergy, bronchodilator and antiasthmatic treatment and prevention drug products and to make recommendations as to the contents of future labeling of such products.

3. Making recommendations to the Food and Drug Administration regarding those ingredients, their amounts, and combinations thereof, which, based upon the available data, could be considered safe and effective for the above stated uses. These recommendations must be in keeping with agency stated definitions of the terms "safe" and "effective" and in keeping with the agency OTC drug combination policy (21 CFR 330.10(a) (4) (iv)).

4. Making recommendations to the Food and Drug Administration regarding those ingredients, their amounts, and combinations thereof, which based upon the available data, are not considered as safe and effective for the above stated uses. The same criteria must apply as in the determinations of those ingredients which are found to be safe and effective.

5. Advising the Food and Drug Administration regarding those ingredients which in their judgment are likely to be safe and effective, but for which more data are needed. In such cases the Panel was requested to give some guidance as to what type of studies and the maximum time period they feel would be adequate to produce such information for future consideration by the Food and Drug Administration.

6. Advising the Food and Drug Administration on the promulgation of a monograph or monographs establishing conditions under which these OTC drug products are generally recognized as safe and effective and not misbranded. This information is submitted in the form of a written report by the Panel containing the following basic recommendations:

a. Listing of the acceptable active ingredients, singly or combinations thereof.

b. Acceptable dosage ranges of these active ingredients and their combinations.

c. A statement of the acceptable indications for use.

d. Recommended labeling guidelines—warnings, precautions, contraindications, directions for use.

* * *

III. Antitussives

A. General Discussion

An antitussive agent specifically inhibits or suppresses the act of coughing. Direct inhibition may result from: depression of medullary or higher centers in the brain; diminishing the sensitivity of the cough receptors in the membranes lining the throat and respiratory passageway; interruption of the transmission of the cough impulses to the brain or to the muscles that are involved in the act of coughing; and by removal of

irritants and excessive secretions through the improvement in bronchial drainage.

In theory, cough suppression may be produced indirectly by one of two mechanisms: A soothing action on the irritated or inflamed throat, which would in effect decrease the sensitivity of special nerve endings or cough receptors in such membranes; and a relief of spasm or localized constriction of the airway. This is known to occur in asthma or following the inhalation of an irritant.

The Panel has followed the presently accepted medical approach and has classified antitussives according to their principal site of action.

1. Centrally acting antitussive agents produce cough suppression by acting on the central nervous system to depress the medullary (brain) cough center and thus raise its threshold for afferent (incoming) cough impulses. These agents may be further subdivided into narcotic antitussives, such as codeine, and nonnarcotic antitussives such as dextromethorphan.

2. Peripherally acting antitussive agents act on the nerve receptors within the respiratory tract. Cough suppression may be produced by several different mechanisms such as a local anesthetic (pain deadening) or analgesic (pain suppressing) action on the mucosa of the respiratory tract; enhancing bronchial airway drainage by reducing the viscosity (thickness) of retained secretions, which may occur with effective expectorant agents or with adequate humidification of the airway; relaxation of the smooth muscle of the bronchial airway in the presence of spasm; or a soothing (demulcent) effect on the irritated throat and bronchial airway walls.

The narcotic antitussives have traditionally been the most effective agents available for suppressing cough. Because of its low abuse potential, codeine, the best known and most widely used antitussive in this group, has been considered safe for OTC use. Except in unusual

circumstances in which cough is associated with pain, e.g., in pleurisy, the more potent narcotics such as morphine are not used because of their potential for acute toxicity from overdosage (respiratory depression) and abuse potential. Such drugs are best administered under medical supervision.

Nonnarcotic antitussives, such as dextromethorphan, act by selective suppression of the central cough mechanism and have no significant abuse liability. Therefore, they would seem to be more advantageous for use in treating cough and also for use in individuals who seem psychologically predisposed to drug dependence.

In general, the antitussives available for OTC use are and should be designed to diminish coughs associated with acute, self-limiting conditions that cause irritation to the respiratory airway. Since it is highly unlikely that such conditions would persist for more than 1 week, the Panel has limited the period of administration of these antitussives to a maximum of 7 days. A persistent cough for more than 1 week or one accompanied by high fever, rash, or persistent headache may be indicative of a serious disease, which should be treated by a physician and does not lend itself to self medication by antitussives. (See part II, paragraph B.4. above—Cough.) In asthma, bronchitis, pulmonary emphysema, and a number of other respiratory diseases, there is often an over production of secretions which accumulates in the airway and results in a cough productive of thick sputum. The suppression of cough by antitussives in such instances would impair clearing of the airway and could be harmful.

References

(1) Jaffee, J. H., "Narcotic Analgesics," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, p. 271, 1970.

(2) "Handbook of Non-Prescription Drugs—1973," American Pharmaceutical Association, Washington, D. C., pp. 15-25, 1973.

(3) Bickerman, H. A., "Antitussive Drugs," *in* "Drugs of Choice, 1974-1975," Edited by Modell, W., The C. V. Mosby Co., St. Louis, pp. 402-408, 1974.

Labeling

Consumers often have difficulty understanding the intended meaning of OTC drug labeling. The Panel concludes that use of vague words, or words which imply a greater effectiveness than other similar OTC products, is false and misleading. The Panel has reviewed the labeling that was submitted for antitussives and for other pharmacologic groups and has attempted to explain why some labeling is acceptable, objectionable, or questionable.

In the case of antitussives, the Panel has reviewed the symptoms of cough and the mechanisms by which the physiologic response is produced. Cough occurs in healthy individuals as a mechanism for clearing the airway of any obstructing mucus or inhaled foreign material. As indicated above, medications that suppress the act of coughing by reducing the number of coughs and/or the intensity of coughing are known as antitussive drugs. Based upon the previous discussion of cough and the discussion of antitussives, the Panel concludes that the following indications are acceptable labeling claims for generally recognized safe and effective antitussives (cough suppressants) for the temporary relief of cough: "Cough suppressant which temporarily reduces the impulse to cough". "For the temporary relief of coughs due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants". "Temporarily quiets coughing by its antitussive action". "Temporarily helps you cough less". "Temporarily helps to quiet the cough reflex that causes coughing".

Because of the lack of clinical studies in children under 2 years of age, the Panel was unable to determine an OTC dose for this age group. Based upon the lack of available data, the Panel recommends the following warning for products containing antitussives: "Do not give this product to children under 2 years except under the advice and supervision of a physician".

Since a persistent or chronic cough may be a sign of a serious condition requiring medical intervention and should be brought to the attention of a physician, the Panel recommends that all labeling for antitussive products bear the following warning: "*Caution:* A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur, or is accompanied by high fever, rash or persistent headache, consult a physician".

In asthma, bronchitis, pulmonary emphysema, and a number of other respiratory diseases, there is often an overproduction of secretions, which accumulate in the airways and results in a cough that produces thick mucus. The suppression of cough by antitussives in such instances would impair clearing of the airway and could be harmful; therefore, the Panel recommends the following additional "*Warning*": "Do not take this product for persistent cough such as occurs with smoking, asthma, emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a physician".

B. CATEGORIZATION OF DATA

1. *Category I conditions under which antitussive ingredients are generally recognized as safe and effective and are not misbranded.*

Category I–active ingredients

The Panel has classified the following antitussive active ingredients as generally recognized as safe and effective and not misbranded:

Codeine preparations: Codeine, Codeine alkaloid, Codeine phosphate, Codeine sulfate
Dextromethorphan
Dextromethorphan hydrobromide
Diphenhydramine hydrochloride

* * *

c. *Diphenhydramine hydrochloride.* The Panel concludes that diphenhydramine hydrochloride is safe and effective for OTC use as an antitussive as specified in the dosage section discussed below.

(1) *Safety.* Diphenhydramine was the first of the antihistamines to be developed in the U.S. and was first used in 1946, clinically, for the relief of a wide variety of allergic symptoms. Diphenhydramine had a low order of toxicity in laboratory animals combined with a high degree of antihistaminic action. The Panel reviewed a number of studies contained in the submissions (Refs. 1 and 2) and concluded that with the exception of sedation, adverse effects have been rare and the drug is safe. The Panel has also found the drug to be safe for use as an antihistamine and this use is discussed elsewhere in this document. (See part VII, paragraph B.1c. below —Diphenhydramine hydrochloride.)

Clinical experience indicates that about 50 percent of persons have drowsiness as a side effect when 50 mg is given (Ref. 3). A double-blind controlled study in 20 males showed no evidence of interference with tests for memory, rotary pursuit, or reaction time with diphenhydramine hydrochloride in doses of 12.5 and 25 mg (Ref. 4). In a double-blind controlled subjective study on 546 patients with acute upper respiratory

infection, drowsiness was reported in 11 of 269 patients receiving 25 mg diphenhydramine 4 times daily over a 3 day period (Ref. 5). Two of 277 patients receiving placebo also reported drowsiness. In infants, high doses of diphenhydramine may cause excitement and convulsions (Ref. 1). The acute toxicity of diphenhydramine in a variety of animal species is similar to other antihistamines such as pyribenzamine (Ref. 6). In children, 20 to 30 tables [*sic*] or capsules containing 50 mg each may represent a lethal or near lethal dose (Ref. 3).

The Panel has recommended specific warnings (see below) because an atropine-like effect is described by patients which includes a drying sensation of the mouth and nose and difficulty with urination in patients with enlarged prostates.

The Panel is aware that recently there was some concern expressed about the potential for misuse and abuse of diphenhydramine. This concern was contained in the statement of the Commissioner of Food and Drugs, which was included in the preamble to the report of the OTC Advisory Panel on Sedatives, Tranquilizers and Sleep-Aid Drug Products and published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292). This Panel will not attempt to comment on the findings of the other Panel or on the societal impact or abuse potential of diphenhydramine when used as an OTC night-time sleep-aid. However, after a review of all the available data, the Panel concluded that diphenhydramine, as well as the other antihistamines reviewed, have a very low abuse potential and that there is little if any evidence of tolerance or habituation. However, the Panel does recognize that doses of diphenhydramine higher than those recommended for OTC use are likely to result in some side effects but that these side effects are sufficient to discourage abuse or misuse. In addition, the two pharmacologic groups for which this Panel is

recommending diphenhydramine for OTC use, i.e., as an antitussive and as an antihistamine, are not recognized as being abusable by the drug abusing subculture. It should also be noted that diphenhydramine is available without a prescription for use as an antihistamine in Canada, the United Kingdom, and many other industrialized countries of the world. The Panel was unable to determine that significant abuse of this ingredient was a problem in any of these countries.

The Panel concludes that diphenhydramine hydrochloride is safe for OTC use as an antitussive in the dosage ranges described below.

(2) *Effectiveness.* A number of animal studies employing chemical and mechanical methods for inducing cough (Refs. 7 through 9), including stimulation of the superior laryngeal nerve, the nerve that supplies the larynx and upper airway (Ref. 10), have demonstrated a reduction in cough frequency, which ranges from 25 percent to 120 percent of that produced by codeine depending on the species of animal employed and the method for inducing cough. The exact mechanism of action of diphenhydramine is not precisely known. However, because of its ability to inhibit the cough reflex resulting from stimulation of the superior laryngeal nerve, the Panel believes a central site of activity of diphenhydramine is a reasonable mode of action. Furthermore, the animal studies are cited as evidence that cough inhibition is not due to a general depression of the central nervous system but to a specific action, similar to codeine, on the "cough center".

Studies in man have consisted of: Experimentally induced cough employing a controlled double-blind crossover design in which both the 25 and 50 mg dose of diphenhydramine hydrochloride produced significant cough suppression equivalent to 15 mg of codeine (Refs. 11 through 13); two double-blind controlled objective

studies in chronic cough, which showed antitussive activity for both 25 and 50 mg diphenhydramine hydrochloride as compared with placebo (Refs. 14 and 15), and the most common adverse reaction was drowsiness; controlled subjective study in chronic cough (Ref. 16) demonstrating antitussive activity superior to placebo but less than codeine; two subjective studies in acute upper respiratory infections, one controlled and one uncontrolled (Refs. 5 and 17), yielding equivocal results; and two objective cough counting studies in chronic cough, which were uncontrolled and showed a decrease in cough with all treatments (Refs. 18 and 19).

While drowsiness did not appear to be a major problem in the single dose studies, it is quite conceivable that repetitive doses may cause profound drowsiness in susceptible individuals. Furthermore, the drying effect of the drug's antihistaminic action could hinder bronchial drainage in patients with productive cough by making the secretions thicker and more difficult to expectorate.

(3) *Dosage.* Adult oral dosage is 25 mg ever 4 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 mg every 4 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is indentified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III, paragraph B.1 below—Category I Labeling.) In addition, the Panel recommends the following specific labeling claims referable to a central mechanism of action and its nonnarcotic designation: (i) *Indications. (a)* "Calms the cough control center and relieves coughing".

(b) "Non-narcotic cough suppressant for the temporary control of coughs".

(c) "Calms cough impulses without narcotics".

(ii) *Warnings. (a)* "May cause marked drowsiness".

(b) "May cause excitability especially in children".

(c) "Do not take this product if you have glaucoma or have difficulty in urination due to enlargement of the prostate gland except under the advice and supervision of a physician".

(d) "*Caution.* Avoid driving a motor vehicle or operating heavy machinery".

(e) "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(iii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 6.25 mg every 4 hours not to exceed 37.5 mg in 24 hours.

References

(1) Wyngaarden, J. and H. Seevers, "The Toxic Effects of Antihistaminic Drugs," *The Journal of the American Medical Association,* 145:277-282, 1951.

(2) Goldstein, L., H. B. Murphree and C. C. Pfeiffer, "Comparative Study of EEG Effects of Anthistamines in Normal Volunteers," *Journal of Clinical Pharmacology,* 8:42-53, 1968.

(3) Douglas, W. W., "Histamine and Antihistamines," *in* "The Pharmacological Basis of Therapeutics." 3rd Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co. New York, p. 635, 1965.

(4) OTC Volume 040224.

(5) Memo to Imboden, Jr., C. A. from A. J. Dresner, M. L. Vanderpool, and M. Jamar-Hirsch,

"Final Summarization of Data from Protocol 266-17, a Multi-Center Study of the Antitussive Efficacy of Benylin Expectorant in the Common Cold," Reference from Presentation to the FDA Review Panel on Over-the-Counter Cough and Cold Preparations, January 8, 1974, is included in OTC Volume 040298.

(6) Loew, E. R., "Pharmacology of Antihistamine Compounds," *Physiological Reviews,* 27:542, 1947.

(7) Wax, J., C. V. Winder and G. Peters, "An Antitussive Property of Diphenhydramine in Dogs. (27591)," *Proceedings of the Society for Experimental Biology and Medicine,* 110:600-603 1962.

(8) Ferguson, H. C., "Personal Communication," Reference from Presentation to the FDA Review Panel on Over-the-Counter Cough and Cold Preparations, January 8, 1974, is included in OTC Volume 040298.

(9) Takagi, K. et al., "Studies on Antitussives. IV. Various Drugs and w-(Diphenylmethoxy) alkylamine Compounds," (English translation), *Journal of the Pharmaceutical Society of Japan,* 81:261-265, 1961.

(10) Eddy, N. B. et al., "Codeine and Its Alternates for Pain and Cold Relief. 4. Potential Alternatives for Cough Relief," *Bulletin of the World Health Organization,* 40:682, 1969.

(11) Bickerman, H. A., "Evaluation of the Antitussive Activity of CI-184, CI-265 and CI-260 Using Citric Acid Aerosols to Induce Cough in Healthy Human Subjects," Reference from Presentation to the FDA Review Panel on Over-the Counter Cough and Cold Preparations, January 8, 1974, is included in OTC Volume 040298.

(12) Bickerman, H. A., "An Evaluation of the Antitussive Activity of 3 Liquid Preparations Employing Citric Acid Challenge to Elicit Cough in Healthy Subjects," Reference from Presentation to FDA Review

Panel on Over-the-Counter Cough and Cold Preparations, January 8, 1974, is included in OTC Volume 040298.

(13) Rodgers, J. M., "Evaluation of the Antitussive Activity of 4 Liquid Preparations Employing Citric Acid Challenge to Elicit Cough in Healthy Subjects." Reference from Presentation to FDA Review Panel on Over-the-Counter Cough and Cold Preparations, January 8, 1974, is included in OTC Volume 040298.

(14) Lilienfield, L. S., "A Study of the Antitussive Effect of Diphenhydramine (Benadryl) in Patients with Chronic Cough," Presentation to the FDA Review Panel on Over-the-Counter Cough and Cold Preparations, June 12, 1974, Appendix A, is included in OTC Volume 040298.

(15) Summer, W. R., "A Study of the Antitussive Effect of Diphenhydramine Hydrochloride (Benadryl) in Patients with Chronic Cough," Presentation to the FDA Review Panel on Over-the-Counter Cough and Cold Preparations, June 12, 1974, Appendix A, is included in OTC Volume 040298.

(16) Cass, L, J. and W. S. Frederik, "The Clinical Evaluation of Silomat as an Antitussive." *Current Therapeutic Research,* 6:14-20, 1964.

(17) Burke, F. and J. Wershing, "Collection of Unpublished Data in Regard to Protocol 266-9," Reference from Presentation to the FDA Review Panel on Over-the-Counter Cough and Cold Preparations, January 8, 1974, is included in OTC Volume 040298.

(18) Brumby, K. H., "Final Summarization and Evaluation of Data from Protocol MUN/302," Reference from Presentation to the FDA Review Panel on Over-the-Counter Cough and Cold Preparations, January 8, 1974, is included in OTC Volume 040298.

(19) Husen, J. H., "Final Summarization and Evaluation of Data from Protocol MUN/304," Reference from Presentation to the FDA Review Panel on Over-the-Counter Cough and Cold Preparations, January 8, 1974, is included in OTC Volume 040298.

Category I Labeling

The Panel recommends the following Category I labeling for antitussive active ingredients to be generally recognized as safe and effective and not misbranded as well as the specific labeling discussed in the individual ingredient statements:

a. *Indications.* (1) "Cough suppressant which temporarily reduces the impulse to cough".

(2) "For the temporary relief of cough due to minor throat and bronchial irritation as may occur with the common cold (cold) or with inhaled irritants".

(3) "Temporarily quiets coughing by its antitussive action".

(4) "Temporarily helps you cough less".

(5) "Temporarily helps to quiet the cough reflex that causes coughing".

b. *Warnings.* (1) "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(2) "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a physician".

(3) "*Caution:* A persistent cough may be a sign of serious condition. If cough persist for more than 1 week, tends to recur or is accompanied by high fever, rash or persistent headache, consult a physician".

* * *

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)) and the Administrative Procedure Act (secs. 4, 5, 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)) and under authority delegated to him (21 CFR 5.1), (recodification published in the FEDERAL REGISTER of June 15, 1976 (41 FR 24268)) the Commissioner of Food and Drugs proposes that Subchapter D be amended by adding a new Part 341 to read as follows:

PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR AND ANTIASTHMATIC PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Subpart B—Active Ingredients

Subpart C—Testing Procedures

Subpart D—Labeling

AUTHORITY: SECS. 201, 502, 505, 701, 52 Stat. 1040-42 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371); (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—General Provisions

§ 341.1 Scope.

An over-the-counter cold, cough, allergy, bronchodilator or antiasthmatic product in a form suitable for oral, inhalant, or topical administration is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in § 330.1 of this chapter.

§ 341.3 Definitions.

As used in this part:

(a) *Age (dosage) range.* Infant or baby (under 2 years), child (2 years to under 12 years), and adult (12 years and over).

(b) *Allergy product.* A drug product used for the relief of the symptoms of allergic rhinitis (such as hay fever).

(c) *Antiasthmatic drug.* A drug product used for the control of the symptoms of bronchial asthma.

(d) *Anticholinergic drug.* A drug used for the relief of excessive secretions of the nose and eyes, symptoms commonly associated with hay fever, allergy, rhinitis, and the "common cold" (cold).

(e) *Antihistaminic drug.* A drug used for the relief of the symptoms of mild allergic rhinitis (such as hay fever) (seasonal allergic rhinitis) and perennial allergic rhinitis.

(f) *Antitussive drug.* A drug which inhibits, controls or suppresses the act of coughing.

(g) *Asthma product.* A drug product used for the control of the symptoms of bronchial asthma.

(h) *Bronchodilator drug.* A drug used to overcome spasms that cause narrowing of the bronchial air tubes, such as in the symptomatic treatment of the wheezing and shortness of breath of asthma.

(i) *Cough product.* A drug product used to inhibit, control or suppress the act of coughing.

(j) *Expectorant drug.* A drug used to promote or facilitate the removal of secretions from the respiratory airways.

(k) *Hay fever product.* A drug product used for the relief of the symptoms of allergic rhinitis (such as hay fever).

(l) *Inhalant dosage.* The dosage range that is generally recognized as safe and effective inhaled nasally or by mouth.

(m) *Nasal decongestant drug.* A drug which reduces nasal congestion caused by acute or chronic rhinitis.

(n) *Oral dosage.* The dosage range that is generally recognized as safe and effective by mouth.

(o) *Topical dosage.* The dosage range that is generally recognized as safe and effective applied topically, such as by external rub for inhalation, as a lozenge for local application by mouth, or as drops or sprays for local application intranasally.

Subpart B—Active Ingredients

* * *

§ 341.14 Antitussives.

The active ingredients of the product consist of the following within the dosage limit established for each ingredient:

(a) *Codeine preparations (codeine, codeine alkaloid, codeine phosphate, codeine sulfate).* (1) Adult oral dosage is 10 to 20 mg every 4 to 6 hours not to exceed 120 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 to 10 mg every 4 to 6 hours not to exceed 60 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 to 5 mg every 4 to 6 hours not to exceed 30 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(2) Shall apply to products pursuant to the requirements identified in § 329.20(a) and § 1308.15(b) of this chapter.

(b) *Dextromethorphan, dextromethorphan hydrobromide.* Adult oral dosage is 10 to 20 mg every 4 hours or 30 mg every 6 to 8 hours not to exceed 120 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 to 10 mg every 4 hours or 15 mg every 6 to 8 hours not to exceed 60 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 to 5 mg every 4 hours or 7.5 mg every 6 to 8 hours not to exceed 30 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(c) *Diphenhydramine hydrochloride.* Adult oral dosage is 25 mg every 4 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 mg every 4 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(c). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

* * *

Subpart D—Labeling

§ 341.50 Labeling of cold, cough, allergy, bronchodilator, and antiasthmatic products.

(a) *Indications.* (1) The labeling shall identify the product pursuant to the appropriate definition(s) established in § 341.3 and shall contain the applicable labeling for the active ingredient(s) as set forth in §§ 341.70, 341.72, 341.74, 341.76, 341.78, and 341.80.

(2) In addition, labeling may also contain the following indication(s): *Provided*, That such phrase(s) is combined and contiguous with the indications required as set forth in § 341.50(a)(i):

(i) "as may be associated with the common cold (cold)."

(ii) "as may occur in the common cold (cold)."

(b) *Directions for use.* The labeling of the product contains the recommended dosage and appropriate directions identified under §§ 341.12, 341.14, 341.16, or 341.20 under the heading "Directions," per time interval, e.g., every 4 hours, or other time period, e.g., 3 times daily, broken down by age groups, if appropriate, followed by "or as directed by a physician."

(c) *Warnings.* The labeling of the product contains the appropriate warning(s) under §§ 341.70, 341.72, 341.74, 341.76, 341.78, or 341.80 and, if applicable, the following general warning under the heading "Warning," which may be combined to eliminate duplicative words or phrases so the resulting warning is clear and understandable. For products containing an alcoholic content greater than 10 percent (weight/weight) "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(d) *Drug interaction precautions.* The labeling of the product, where appropriate under § 341.76 or § 341.80, contains drug interaction precautions, under the heading "Drug Interaction Precautions".

* * *

§ 341.74 Products containing antitussives.

(a) *Indications.* The labeling of the product may contain any of the following indications, under the heading "Indications": (1) "Cough suppressant which temporarily reduces the impulse to cough".

(2) "For the temporary relief of cough due to minor throat and bronchial irritation as may occur with the common cold (cold) or with inhaled irritants".

(3) "Temporarily quiets coughing by its antitussive action".

(4) "Temporarily helps you cough less".

(5) "Temporarily helps to quiet the cough reflex that causes coughing".

(6) For products containing an ingredient identified in § 341.14(a): "Calms the cough control center and relieves coughing".

(7) For products containing an ingredient identified in § 341.14(b) and (c):

(i) "Calms the cough control center and relieves coughing".

(ii) "Non-narcotic cough suppressant for the temporary control of coughs".

(iii) "Calms cough impulses without narcotics".

(b) "*Warnings.* The labeling of the product contains the following warnings, under the heading "Warnings": (1) "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(2) "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a physician".

(3) "*Caution:* A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur or is accompanied by high fever, rash or persistent headache, consult a physician".

(4) For products containing an ingredient identified in § 341.14(a):

(i) "May cause or aggravate constipation".

(ii) "Do not give this product to children taking other drugs except under the advice and supervision of a physician".

(iii) "Do not take this product if you have a chronic pulmonary disease or shortness of breath except under the advice and supervision of a physician".

(5) For products containing an ingredient identified in § 341.14(c): (i) May cause marked drowsiness".

(ii) "May cause excitability especially in children".

(iii) "Do not take this product if you have glaucoma or have difficulty in urination due to enlargement of the prostate gland except under the advice and supervision of a physician".

(iv) "Caution: Avoid driving a motor vehicle or operating heavy machinery".

(v) "Do not give this product to children under 6 years except under the advice and supervision of a physician".

* * *

Interested persons are invited to submit their comments in writing (preferably in quintuplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal on or before December 8, 1976. Such comments should be addressed to the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852, and

may be accompanied by a memorandum or brief in support thereof. Additional comments replying to any comments so filed may also be submitted on or before January 7, 1977. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: July 30, 1976.

SHERWIN GARDNER,
Acting Commissioner of
Food and Drugs.

APPENDIX G

IN THE
DISTRICT COURT OF THE UNITED STATES
FOR THE DISTRICT OF SOUTH CAROLINA
GREENVILLE DIVISION

Civil Action No. 70-1001

O'NEAL, JONES & FELDMAN, INC., BENTEX PHARMACEUTICALS, INC., SARON PHARMACAL CORP., MORTON PHARMACEUTICALS, INC., EDWARDS PHARMACAL COMPANY, E. W. HEUN COMPANY, GERIATRIC PHARMACEUTICAL CORP., C. S. RUCKSTUHL COMPANY, WINSTON PHARMACEUTICALS, INC., WABASH PHARMACEUTICALS, INC., SOUTHERN DRUG & MFG. CO., THE BLAINE COMPANY, BROWN PHARMACEUTICAL CO., MAYRAND, INC. PHARMACEUTICAL ASSOCIATES, INC., HALSOM DRUG COMPANY, PISGAH PHARMACEUTICALS, INC., BCR PHARMACAL CO., INC., ALTO PHARMACEUTICALS, INC., PAN-AMERICAN LABORATORIES, INC., PHILLIPS LABORATORIES, INC., PRITCHARD PHARMACEUTICAL PRODUCTS, INC., FOS PHARMACEUTICAL CO., W. E. BOODY & CO.,

Plaintiffs,

vs.

ELLIOT P. RICHARDSON, Secretary of the Department of Health, Education and Welfare and CHARLES C. EDWARDS, Commissioner of the Food and Drug Administration.

Defendants.

ORDER

This is a civil action for declaratory and injunctive relief brought by twenty-four pharmaceutical companies aggrieved by the action of the Food and Drug Administration (hereinafter F.D.A.) respecting drugs containing

pentylenetetrazol. The events leading to the commencement of this action may be summarized as follows: In August 1969 the F.D.A. announced in the FEDERAL REGISTER its intention to initiate proceedings to withdraw approval of new drug applications for two drugs containing pentylenetetrazol and nicotinic acid. (34 F.R. 13673) The drugs covered by those applications differed from those manufactured by the plaintiffs herein in that the product covered by one application was injected intravenously and the other application contained a third active ingredient, reserpine. The published notice invited the submission of data on the efficacy of the products by any interested person who might be adversely affected by the removal from the market of the drugs covered by the new drug applications. The notice further stated:

> Promulgation of the proposed order will cause any drug for human use containing the same active substances to be a new drug for which an approved new-drug application is not in effect. Any such drug then on the market would be subject to regulatory proceedings.

None of the plaintiffs herein responded to the notice and in May, 1970, a second notice was published stating that substantial evidence of the effectiveness of the drugs covered by the new drug applications has not been provided and that the approval of the applications would be withdrawn. Notice was also given that any affected person desirous of a hearing on the question should so elect within 30 days (35 F.R. 7749). That notice contained language concerning the effect on drugs other than those covered by the applications to be withdrawn substantially identical to the language of the August notice set out above.

In September 1970 the F.D.A. published its order withdrawing approval of the two new drug applications mentioned above and directing the recall of outstanding stocks of the drugs. 35 F.R. 14412.

Pursuant to its revocation of the two new drug applications, the F.D.A. took steps to effect the removal from the market of drugs containing pentylenetetrazol manufactured by various of the plaintiffs. By their complaint in this action the plaintiffs seek declaratory judgment determining the validity and enforceability of the order of the Secretary as it concerns their drugs and injunctive relief pendent lite. The defendant moves that the action be dismissed for want of jurisdiction and failure to state a claim for which relief can be granted.

The Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, *et seq.*) effective in 1938, gave preclearance authority to the Food and Drug Administration to regulate the distribution of new drugs by a system of new-drug applications which had to be obtained before distribution of the new drug in interstate channels was allowed. The early definition of new drugs, however, gave the Agency power to regulate these drugs and approve them on the basis of safety alone. The drug companies were not required to support their claims of effectiveness for the drug with appropriate medical data. Effective on October 10, 1962, the Act was amended to close this important gap in the regulatory power of the Agency. Under the provisions of the Act as amended, a drug not only must be proved safe, but also must be shown by "substantial evidence," to be effective for the indication and uses described in its labeling. The amendments also define "substantial evidence" as consisting of ". . . adequate and well-controlled investigations, including clinical investigations, by experts . . ." sufficient to demonstrate that the drug works as claimed [21 U.S.C. 355(d)]. The burden of producing evidence of effectiveness to support continued marketing of drugs which have already been cleared on the grounds of safety, is placed squarely on the drug manufacturers and distributors. [21 U.S.C. § 355(b)]. The Act as amended also gives the Secretary power to revoke approved new

drug applications for several reasons among which is failure to submit substantial evidence of the effectiveness of the drug [21 U.S.C. 355(e)3]. It was pursuant to this authority that the Secretary issued the order by which the plaintiffs herein are aggrieved.

The Act grants the Secretary primary jurisdiction to make determinations regarding new drug applications and provides direct appeal from his orders to the circuit courts.[1]

[1]21 U.S.C. § 355(h). An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of the court to the Secretary, or any officer designed by him for that purpose, and thereupon the Secretary shall certify and file in the court the record upon which the order complained of was entered, as provided in section 2112 of title 23, United States Code. Upon the filing of such petition such court shall have exclusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do. The finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive. If any person shall apply to the court for leave to adduce additional evidence, and shall show to the satisfaction of the court that such additional evidence is material and that there were reasonable grounds for failure to adduce such evidence in the proceeding before the Secretary, the Court may order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper. The Secretary may modify his findings as to the facts by reason of the additional evidence so taken, and he shall file with the court such modified findings which, if supported by substantial evidence, shall be conclusive, and his recommendation, if any, for setting aside of the original order. The judgment of the court affirming or setting aside any such order of the Secretary shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of title 28 of the United States Code. The commencement of proceedings under this subsection shall not, unless specifically ordered by the court to the contrary, operate as a stay of the Secretary's order.

The plaintiffs do not contend that this court has jurisdiction to consider the propriety of the Secretary's revocation of the two new drug applications. Rather they argue either that their drugs are not new drugs within the meaning of the Act or are within the grandfather clause;[2] and are therefore not subject to the Secretary's regulation of new drugs. The plaintiffs contend that seizure, injunction, or criminal prosecution by the F.D.A. pursuant to 21 U.S.C. §§ 332-34 is imminent.[3] They urge that, rather than proceeding at their peril, they are entitled to declaratory relief adjudicating the merits of their respective contentions concerning the status of their

[2]21 U.S.C. § 321 (p). The term "new drug" means—

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of the Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such condition, has become so recognized, but which has not, otherwise than in such investigation, been used to a material extent or for a material time under such conditions.

[3]The plaintiff Bentex Pharmaceutical Company received the following letter from the F.D.A.:

Nov. 4, 1970

"This letter is written in reference to your products Benizol Tablets & Elizir, Benizol A-D Tablets, & Benizol Plus capsules & Elixir containing Pentylenetetrazol for human use.

On September 12, 1970, an announcement published in the *Federal Register* setting forth the conclusion of the Food and Drug Administration that there is a lack of substantial evidence that drugs similar to yours are effective for the uses prescribed, recommended, or suggested in their labeling.

drugs.[4] They argue persuasibly that they are entitled to a day in court on that question prior to the seizure of their products and possible criminal prosecution.

The plaintiffs urge that they can only have that day in this court. The court does not agree. The Act gives the F.D.A. authority to proceed by seizure action, criminal prosecution, or injunction, [21 U.S.C. 332-334] to clear the channels of interstate commerce of drugs which have improperly avoided the new drug procedures. This grant of authority to approve or withhold approval of new drug application, or to proceed with regulatory action in the courts, necessarily implies authority for F.D.A. to determine the threshold question of whether the article involved is a drug which requires an approved new drug application for lawful interstate shipment. The determination that a drug is a new drug is essential to any

---

Accordingly, the Commissioner of the Food and Drug Administration has withdrawn approval of the applicable new drug applications for such drugs.

The withdrawal of all previously approved new drug applications causes any similar drug to be a new drug for which an approved new drug application is not in effect. Because these are no longer regarded as legal products, any such drug on the market is subject to regulatory proceedings under the applicable provisions of the Federal Food, Drug, and Cosmetic Act.

We request your reply within 15 days after receipt of this letter stating your intentions with respect to removal of all outstanding stocks of your product to the retail level."

[4]It appears that for a time drugs of the type in question were regarded as old drugs by the F.D.A. The record contains a letter dated Dec. 15, 1958 which reads in pertinent part as follows:

"As to your inquiry concerning the new drug status of a timed disintegration tablet containing Pentylenetetrazol 300 mg., Nicotinic Acid 150 mg.

In our opinion this article is not a new drug as defined in section 201(p) of the Federal Food Drug and Cosmetic Act when distributed as a prescription preparation under the labeling which you have submitted." Statements such as the above were, however, revoked by the Secretary [21 C.F.R. 130.39].

F.D.A. action regulating it by means of new drug applications. Therefore, the F.D.A. must have jurisdiction to make that determination.[5]

The defendant, on the other hand urges that this court does not have jurisdiction to consider and determine the status of the drugs in question, that the F.D.A. has primary and exclusive jurisdiction with appeal to the circuit court. That contention is likewise without merit. There is no doubt that the F.D.A. does have primary jurisdiction to make determinations concerning the safety and effectiveness of new drugs. Its expertise is necessary for consideration of the complex and technical nature of the factual issues to be evaluated.[6] That question is not, however, in dispute in this instance. The contention urged by the defendant that its drugs are old or grandfathered, must turn upon the court's conclusion as to whether among qualified experts there was general recognition of the safety and efficacy of the drug. [*United States* v. *"Quick-O-Ver"*, 274 F. Supp. 443 (1967)]. Counsel for the defendants acknowledged that the fact that the drugs were old or grandfathered would be a defense to be raised and considered in the district court when and if the F.D.A. sought sanctions against the plaintiff manufacturers.

The remaining question regarding the jurisdiction of this court is whether the action for declaratory judgment may be maintained in its present posture. The opinions

---

[5]Hymson, Westcott and Dunning, Inc. v. Fich, C.A. 2112, D.Md., decided September 16, 1970, on facts represented to the court to be similar to the present case held that the F.D.A. could consider and decide questions determining the status of a drug and that review of that determination would be available pursuant to 21 U.S.C. 355(h) set out at n.l, supra.

[6]See e.g. Far East Conference v. United States, 342 U.S. 570 (1952); Tyler Pharmacal Dist. v. H.E.W., 408 F.2d 95 (7th Cir. 1969); Lemmon Pharmacal Co. v. Richardson, C.A. 68-921, E.D. Pa. 1970.

of the Supreme Court in *Abbott Laboratories* v. *Gardner*, 387 U.S. 136 (1967) and *Toilet Goods Asso.* v. *Gardner*, 387 U.S. 158 (1967) convince this court that the present matter is properly before it. As pointed out in those cases, there is nothing in the Food, Drug, and Cosmetic Act [21 U.S.C. § 301, *et seq.*] which bars a pre-enforcement suit under the Administrative Procedure Act [5 U.S.C. §§ 701-704] and the Declaratory Judgment Act [28 U.S.C. § 2201]. The language in the Secretary's announcement of May 20, 1970, of which the plaintiffs complaint and pursuant to which the Secretary apparently intends to proceed against them, is apparently final within the meaning of 5 U.S.C. § 704. (*Abbot*, supra, at 692) The letter of the F.D.A. set out above in note 4, indicates that action against the plaintiffs is imminent. The affidavits of the plaintiffs show that the threatened action will result in substantial injury to them. Therefore, this matter is properly before this court and the defendant's motion to dismiss is denied.

The court indicated above that the F.D.A. has jurisdiction to determine whether the drugs in question are new drugs. The court is of the opinion that, even though that determination can be made in this forum, the nature of the proof revelant to that issue makes the F.D.A. the more able arbiter of the question. However, if such determination is to be binding upon the plaintiffs in this action and the industry in general, parties, interested in the status of drug combinations must be given an opportunity to be heard. They must be provided a day in court on the issue, during which a record can be made, on which record appeal to the circut court can be had. That procedure would produce a resolution to the question which would bind the industry and remove the issue from subsequent, and perhaps numerous, enforcement actions. These plaintiffs quite properly point out that they have as yet had no opportunity to be heard on the question of whether their products are new drugs

within the meaning of the Act; and it does not appear that such hearing could have been required of the F.D.A. by the plaintiffs. Evaluation of conflicting reports as to the reputation of drugs among experts in the field is not a matter well left to a court without chemical or medical background. The court's opinion in this regard has influenced it considerably in its consideration of appropriate temporary relief.

The area of regulation of drugs is one which the court enters with great reluctance. However, the affidavits of the plaintiffs convince the court that they may suffer substantial business losses, perhaps unnecessarily, if the court refuses to grant temporary relief. As the court understands the record before it and the argument of counsel, there is no contention that the use of the plaintiffs' drugs in treatment of the symptoms of senility in geriatric patients is in any way harmful to them, either directly or indirectly by causing the disuse of better drugs. The court's order, being based upon this hypothesis, will be vacated upon a sufficient contrary showing by the defendant and, upon request by the defendant, the court will arrange to hear its proof in that regard.

The situation revealed by the record to date convinces the court that the status quo must be preserved until such time as the plaintiffs have an opportunity to be heard on the merits of their contention. Therefore, the court will enjoin the defendants from instituting actions against the plaintiffs on account of such of their products as are presently marketed, as contain combinations of pentylenetetrazol and nicotinic acid, are distributed by prescription, and are for treatment of symptoms of senility in geriatric patients; and the defendants are hereby enjoined from instituting any action against the plaintiffs herein for the cause stated above until such time as there has been a determination that the products

in question are new drugs. Recognizing the desirability of the F.D.A.'s making such determination, after a hearing of the matter, this court will defer further proceedings herein upon a showing by the defendants that such hearing will be held. It will dissolve the injunction herein ordered, and dismiss the presentation upon resolution of the question by the F.D.A. after a hearing.[7] Should the F.D.A. decline to hold such hearing, the matter must proceed to determination in this court.

AND IT IS SO ORDERED.

ROBERT W. HEMPHILL
Robert W. Hemphill
United States District Judge

Columbia, South Carolina
February 10, 1971

---

[7]A court has considerable discretion in proceeding in actions for declaratory judgment, and may dismiss such actions if they are pending in litigation elsewhere. Abbott Laboratories v. Gardner, 387 U.S. 136, 155 (1952).

APPENDIX H

Text of FDA Telegram of November 24, 1976

TO:
DONALD O'NEILL
PRESIDENT
PARKE DAVIS & COMPANY
JOSEPH CAMPAU AVENUE AT THE RIVER
DETROIT, MICHIGAN 48232

INFO COPY: DETROIT DISTRICT (HFR-5300)
ATTN: R & E COORDINATOR

THIS IS IN REFERENCE TO YOUR PRODUCT, BENYLIN COUGH SYRUP, WHICH YOU INTRODUCED FOR NATIONWIDE OVER-THE-COUNTER MARKETING IN MID 1975.

THERE WAS PUBLISHED IN THE *FEDERAL REGISTER* OF DECEMBER 4, 1975, AND AUGUST 4, 1976, (PROPOSED AND FINAL REGULATIONS RESPECTIVELY), CLARIFICATION OF FDA'S POLICY REGARDING THE MARKETING STATUS OF INGREDIENTS WHICH HAVE BEEN FORMERLY SOLD ONLY BY PRESCRIPTION AND FOR WHICH OTC MARKETING HAD BEEN INITIATED ON THE BASIS OF OTC ADVISORY PANEL FINDINGS. DIPHENHYDRAMINE HYDROCHLORIDE, AMONG OTHER INGREDIENTS, WAS SPECIFICALLY MENTIONED, AND IT WAS STATED THAT THE AGENCY WOULD REVIEW THESE INGREDIENTS TO DETERMINE THEIR REGULATORY STATUS. FURTHER, IN THE PREAMBLE TO THE COUGH, COLD AND ALLERGY PROPOSED OTC MONOGRAPH (*FEDERAL REGISTER*, SEPTEMBER 9, 1976), THERE IS A DISCUSSION OF DIPHENHYDRAMINE WITH THE COMMISSIONER'S CONCLUSION THAT THE MARKETING STATUS OF DIPHENHYDRAMINE HYDROCHLORIDE AS AN ANTITUSSIVE SHOULD BE RESOLVED BY FIRST CONSIDERING THE APPROVABILITY OF THE FIRM'S (PARKE-DAVIS') SUPPLEMENTAL NDA (#6-514/S-007). ALSO, THE NOTICE STATES THAT IF THE SUPPLEMENT IS DENIED, THE COMMISSIONER WILL AT THAT TIME ISSUE A NOTICE IN THE FEDERAL REGISTER STATING HIS DISAGREEMENT WITH THE PANEL'S RECOMMEN-

DATION THAT DIPHENHYDRAMINE HYDROCHLORIDE BE CLASSIFIED IN CATEGORY I FOR OTC ANTITUSSIVE USE. IN THAT EVENT, ANY SUCH PRODUCT MARKETED OTC WOULD THEREUPON BE SUBJECT TO IMMEDIATE REGULATORY ACTION IN ACCORDANCE WITH THE ENFORCEMENT POLICY ANNOUNCED IN THE FEDERAL REGISTER OF AUGUST 4, 1976.

SINCE YOUR SUPPLEMENT TO NDA 6-514/S-007 TO PROVIDE FOR THE OTC MARKETING OF BENYLIN COUGH SYRUP HAS BEEN DISAPPROVED BY LETTER OF SEPTEMBER 8, 1976, AND THE COMMISSIONER IS CAUSING TO BE PLACED IN THE FEDERAL REGISTER HIS DISAGREEMENT WITH THE PANEL AS STATED ABOVE, THE MARKETING STATUS OF THE PRODUCT REVERTS TO THE CONDITIONS FOR MARKETING AS SET FORTH IN NDA-6-514, WHICH LIMITS THE DRUG TO PRESCRIPTION SALE.

IN VIEW OF THIS AND IN THE INTEREST OF THE PUBLIC HEALTH, WE REQUEST THAT YOU IMMEDIATELY DISCONTINUE DISTRIBUTION OF BENYLIN COUGH SYRUP AND UNDERTAKE IMMEDIATE RECALL OF THE ENTIRE OTC DISTRIBUTION OF THE PRODUCT TO THE RETAIL LEVEL.

THE RECALL SHOULD BE ACCOMPLISHED UNDER THE FOLLOWING PROCEDURES:

(1) PARKE, DAVIS IMMEDIATELY UNDERTAKE RECALL OF THE PRODUCT TO THE RETAIL LEVEL INCLUDING NON-PHARMACY OUTLETS.

(2) WE WILL PERMIT PHARMACIES TO PLACE STOCKS OF BENYLIN COUGH SYRUP BEHIND THE COUNTER WHERE IT MAY BE USED TO FILL PRESCRIPTIONS. STOCK IN PHARMACIES MUST BE PROMPTLY RELABELED WITH THE PRESCRIPTION LEGEND AND FULL DISCLOSURE LABELING AS SPECIFIED IN THE APPROVED NDA AND REGULATION 201.200. DISCLOSURE OF DRUG EFFICACY STUDY EVALUATIONS.

(3) STOCK AT THE MANUFACTURER AND WHOLESALERS MUST BE FROZEN UNTIL APPROPRIATELY RELABELED FOR PRESCRIPTION SALE.

(4) STOCK CONTAINING CHLOROFORM RETURNED TO PARKE, DAVIS MAY NOT BE RELABELED AND OFFERED FOR SALE BECAUSE OF THE BAN ON HUMAN DRUGS CONTAINING CHLOROFORM AS DISCUSSED IN THE *FEDERAL REGISTER* OF JUNE 29, 1976.

(5) THE RELABELING OF STOCK IN PHARMACIES AND WHOLESALERS MAY BE ACCOMPLISHED THROUGH THE USE OF PARKE DAVIS' DETAIL MEN OR SALES FORCE.

FDA WILL ISSUE A PUBLIC PRESS STATEMENT ON THIS MATTER IN ADDITION TO ANY CONSUMER NOTIFICATION PARKE DAVIS MAY ELECT TO UNDERTAKE.

OUR DETROIT DISTRICT OFFICE WILL CONTACT YOU PROMPTLY ON THIS MATTER.

JOSEPH P. HILE
ASSOCIATE COMMISSIONER
FOR COMPLIANCE
FOOD AND DRUG ADMINISTRATION